Armed Forces College of Medicine

AFCM

Activation of B lymphocytes

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Humoral Immune response

By the end of this lecture the student will be able to*:*

1. Differentiate between the sequence of B cell activation in T cell dependent & T cell independent antigens

2. Compare between primary and secondary humoral immune response.

3. Discriminate between different isotypes of immunoglobulins regarding structure, distribution and function

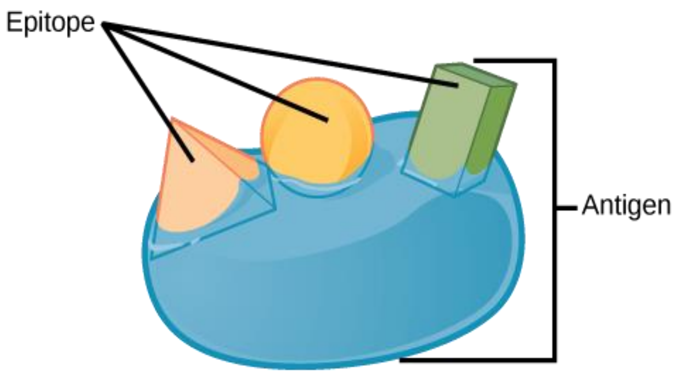
4. Outline monoclonal Abs

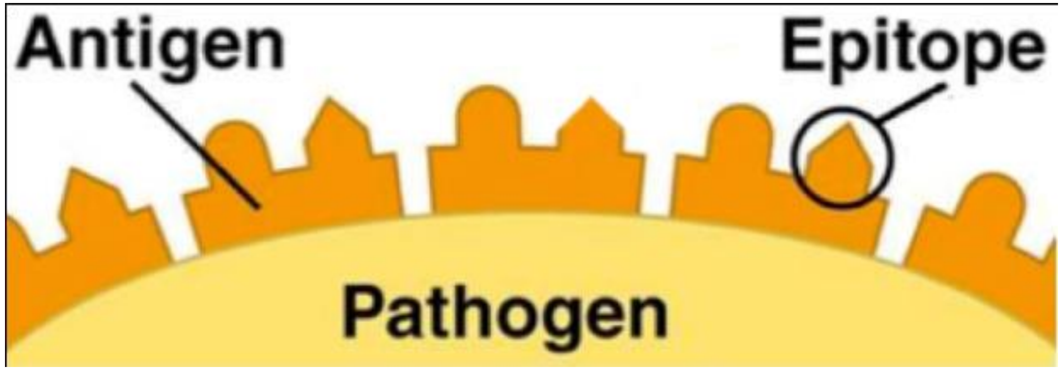
EPITOPE

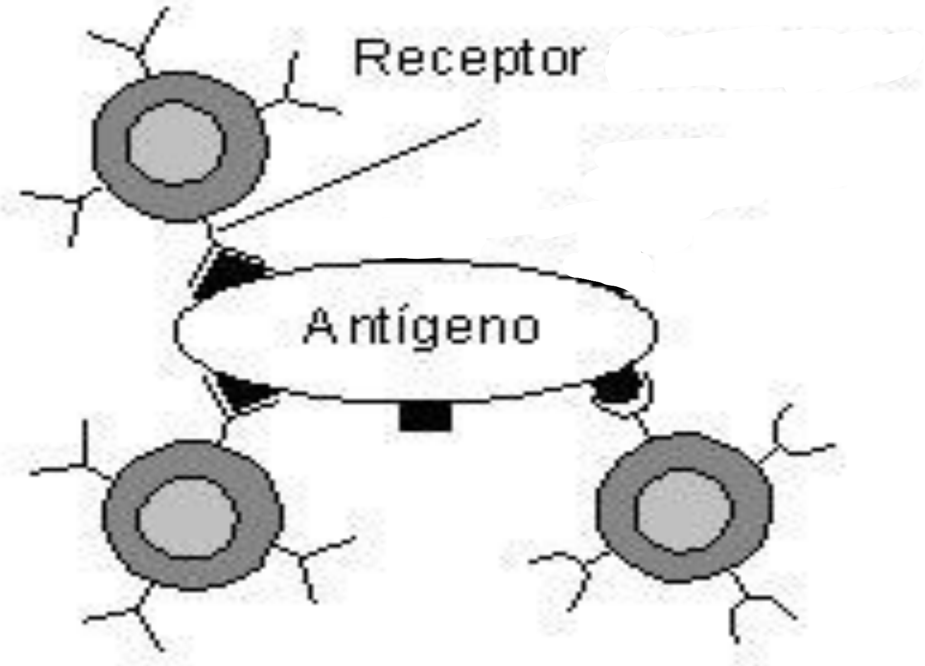
Definition The **smallest biochemical unit** of Antigen that binds specifically **with Ag receptor** on B & T lymphocytes

↓

Stimulation of immune response



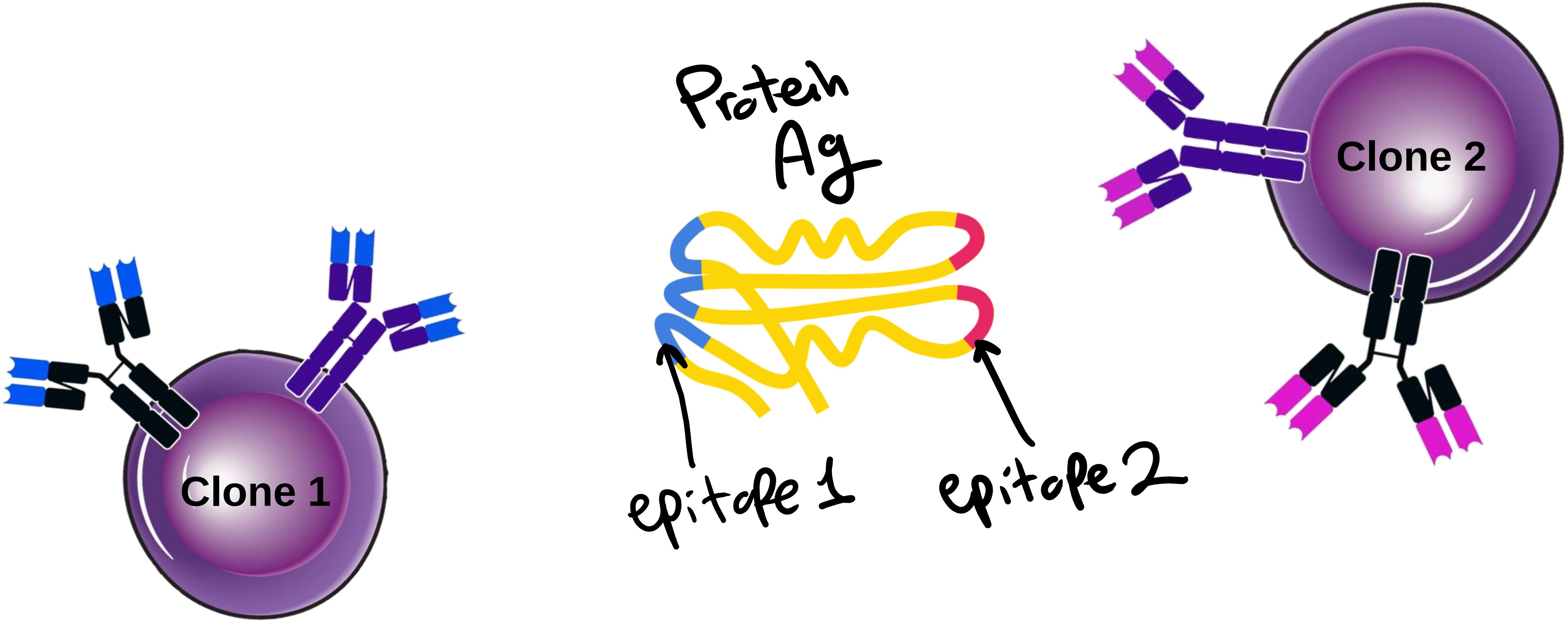




Epitope (antigenic determinant)

1 Ag may have

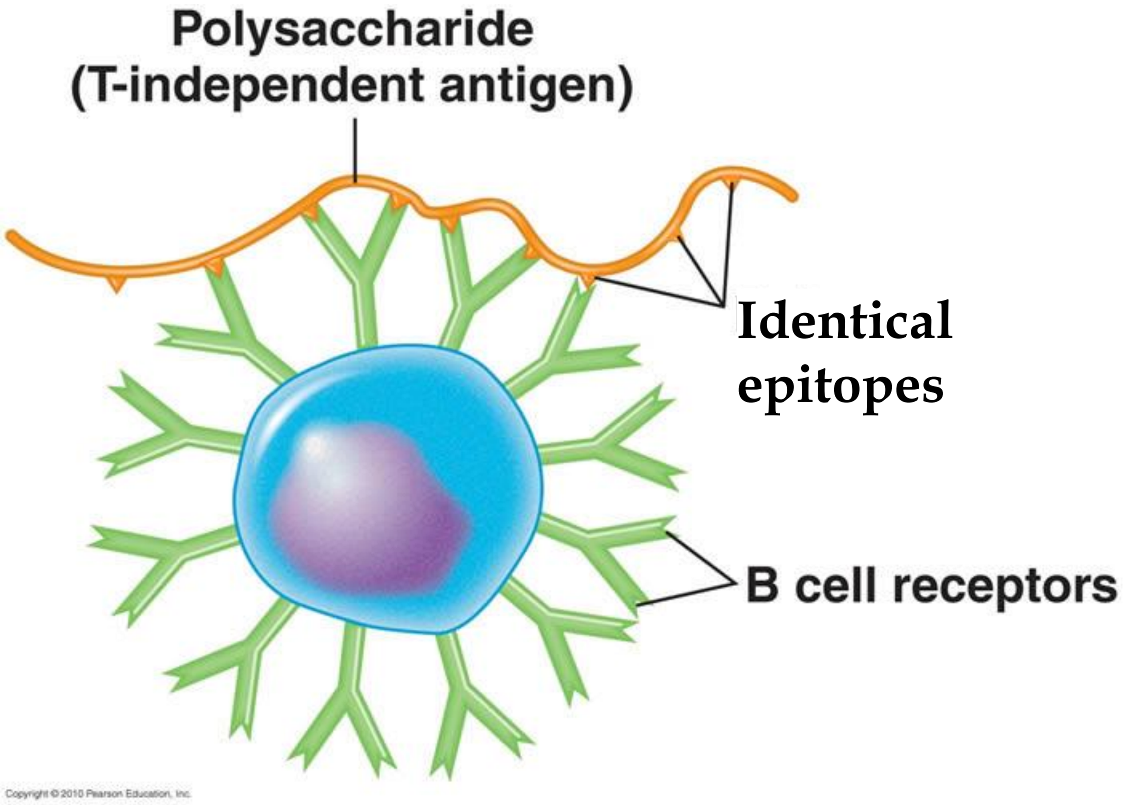
- Several **different** epitopes e.g **protein Ag** → ⊕ **different clones of B cells**



Epitope (antigenic determinant)

1 Ag may have

- Several **different** epitopes e.g **protein Ag** → ⊕ **different clones of B cells**
- Repeating (**identical**) epitopes e.g **polysaccharide of bacteria** → ⊕ **the same (one) clone of B cell**



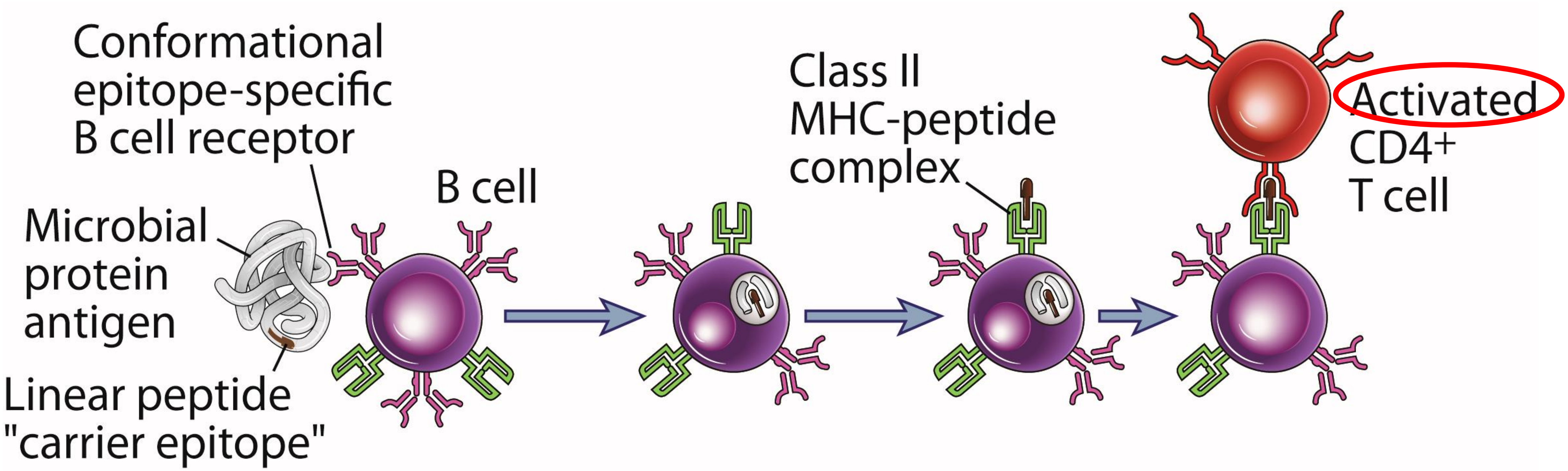
I – Protein Ags : T (thymus) dependent Ags

Need ⊕ of T helper cells to activate B cells ➜ B cells will act as **APCs to Th**

① Ag binds to BCR (IgM or IgD)

➥ Internalized (receptor mediated endocytosis)

➥ Processed & epitopes are associated with **MHC II proteins**



Conformational epitope-specific B cell receptor
B cell
Microbial protein antigen
Linear peptide "carrier epitope"
Class II MHC-peptide complex
Activated CD4+ T cell

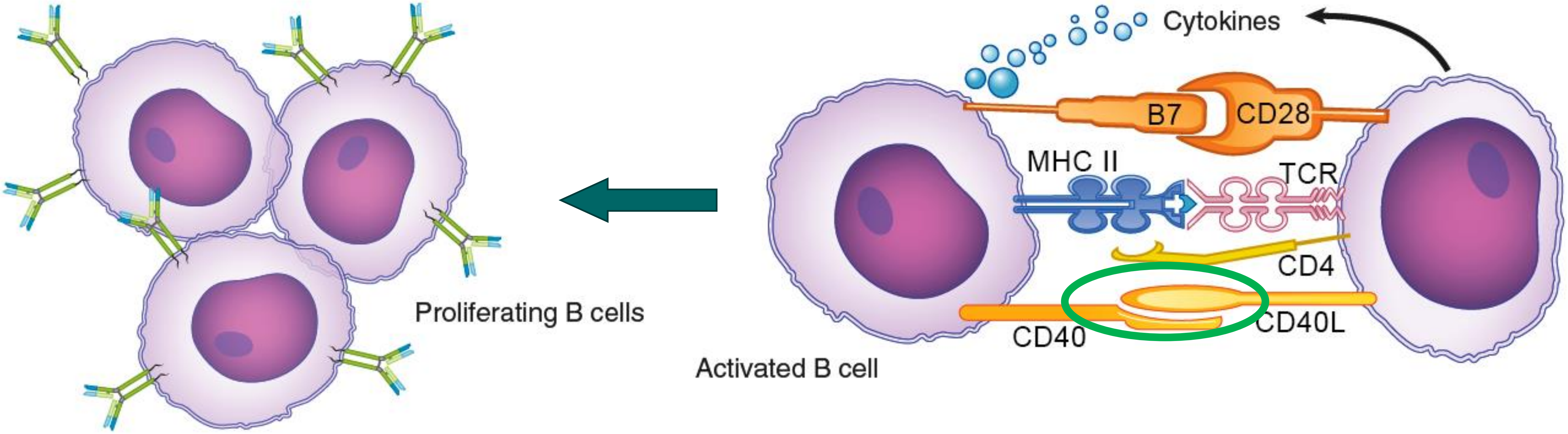
I – Protein Ags : T (thymus) dependent Ags

2 Interaction with activated Th cells

Peptide – MHC class II bind to **TCR complex & CD4**

3 Activation of B cells

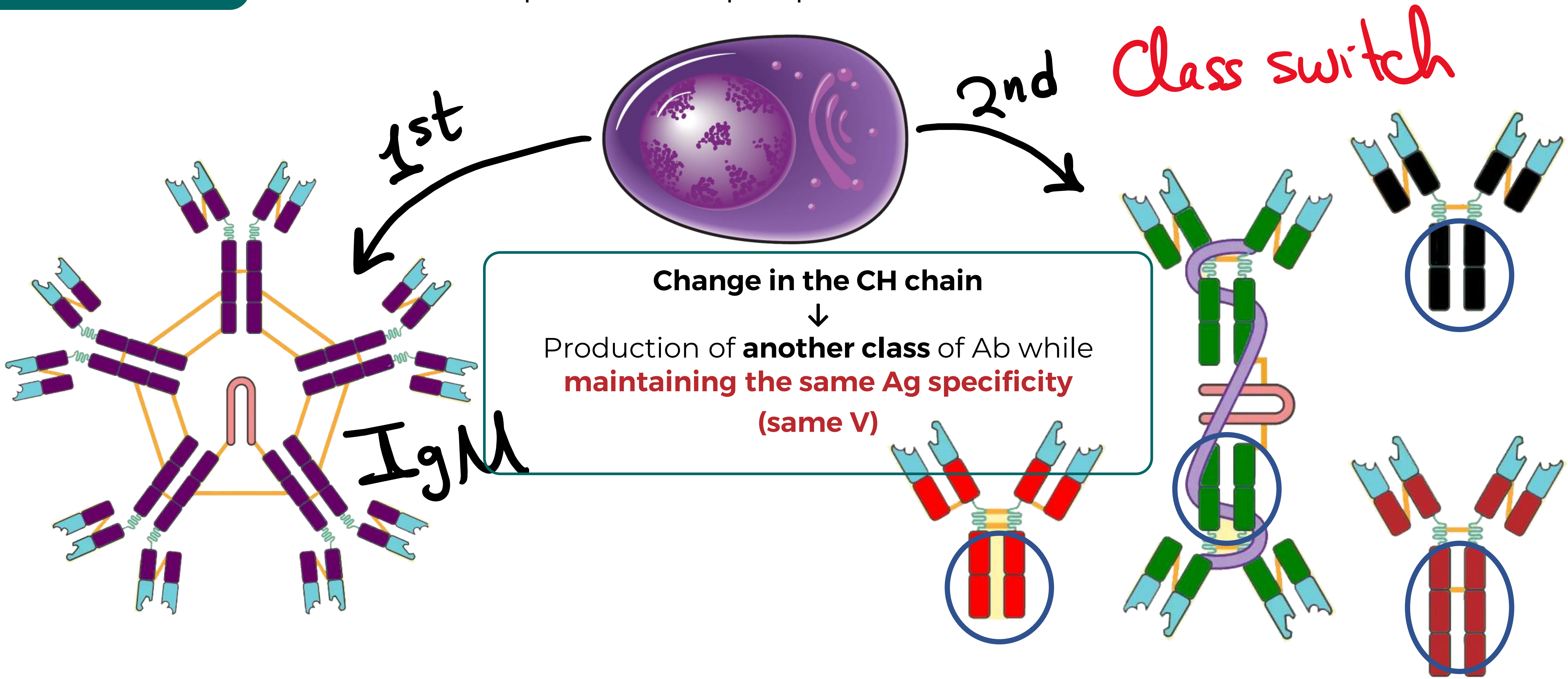
Th produce cytokines → B cells become **activated** → **Clonal expansion**



I - Protein Ags : T (thymus) dependent Ags

4 Differentiation of activated B cells into

A) Plasma cells Produce Abs specific for epitope



Change in the CH chain

↓

Production of **another class** of Ab while **maintaining the same Ag specificity (same V)**

I - Protein Ags : T (thymus) dependent Ags

4 Differentiation of activated B cells into

A) Plasma cells Produce Abs specific for epitope

1st Produce
IgM
(secreted)

2nd : produce other classes by Isotype (class) switch

Mechanism

Change in the CH chain
↓
Production of **another class** of Ab while **maintaining the same Ag specificity (same V)**

Requires 2 signals

CD40 L on activated T cells binds to CD 40 on B cells

Cytokines

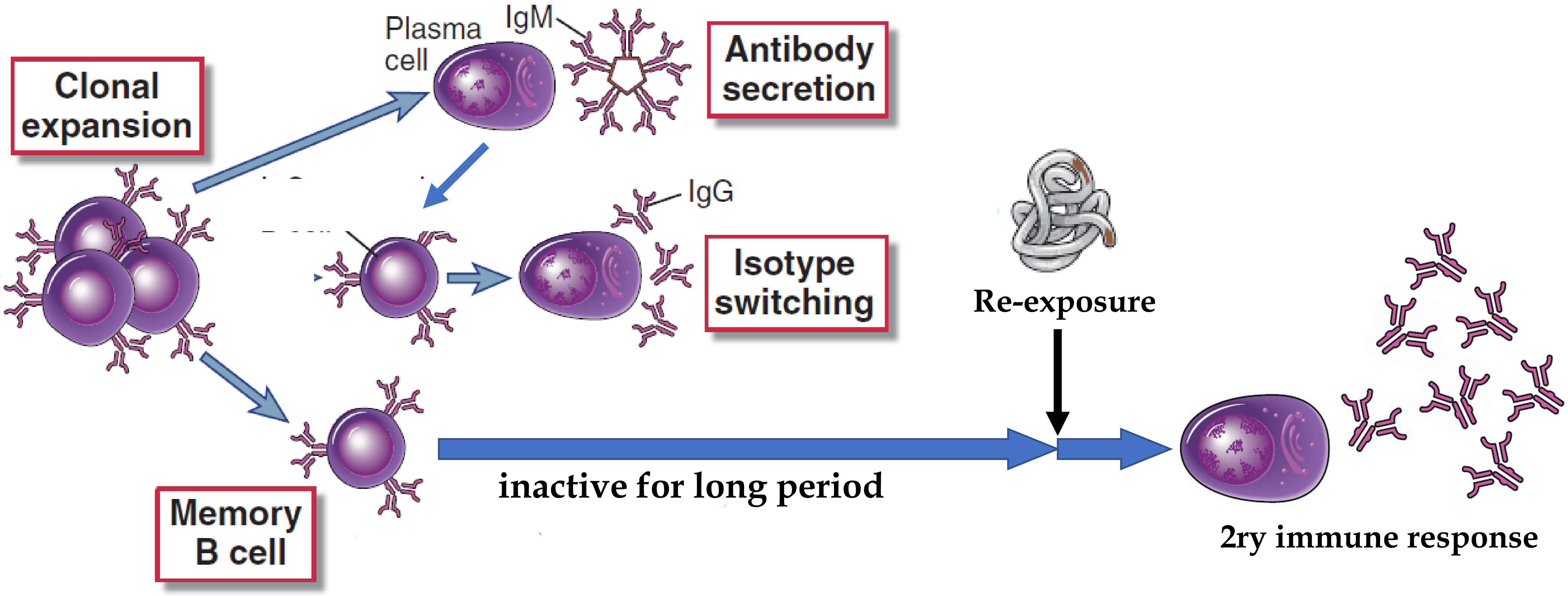
- **IFNγ → IgG**
- **IL-4 & 13 → IgE**

B) Memory cells

- **Remain inactive** for long periods

Formation of memory cells need cytokines & CD40 L from T helper

- **Activated rapidly** on reexposure to same Ag (2ry immune response) → **Rapid & Strong production of Abs**



Clonal expansion

Antibody secretion

Isotype switching

Memory B cell

inactive for long period

Re-exposure

2ry immune response

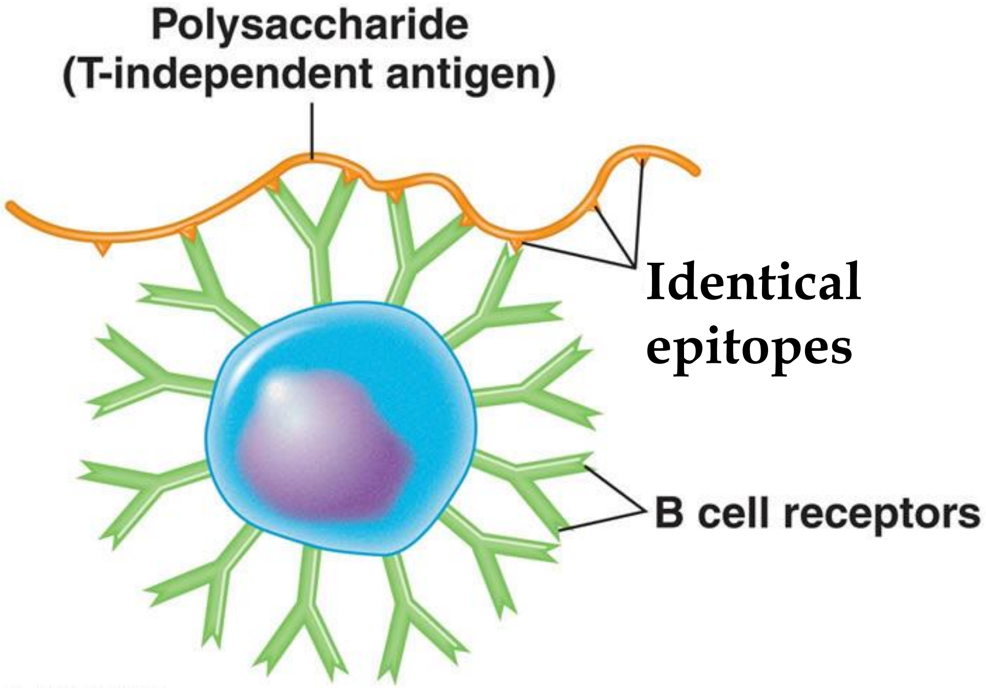
II) Polysaccharide Ags: T (Thymus) independent Ags

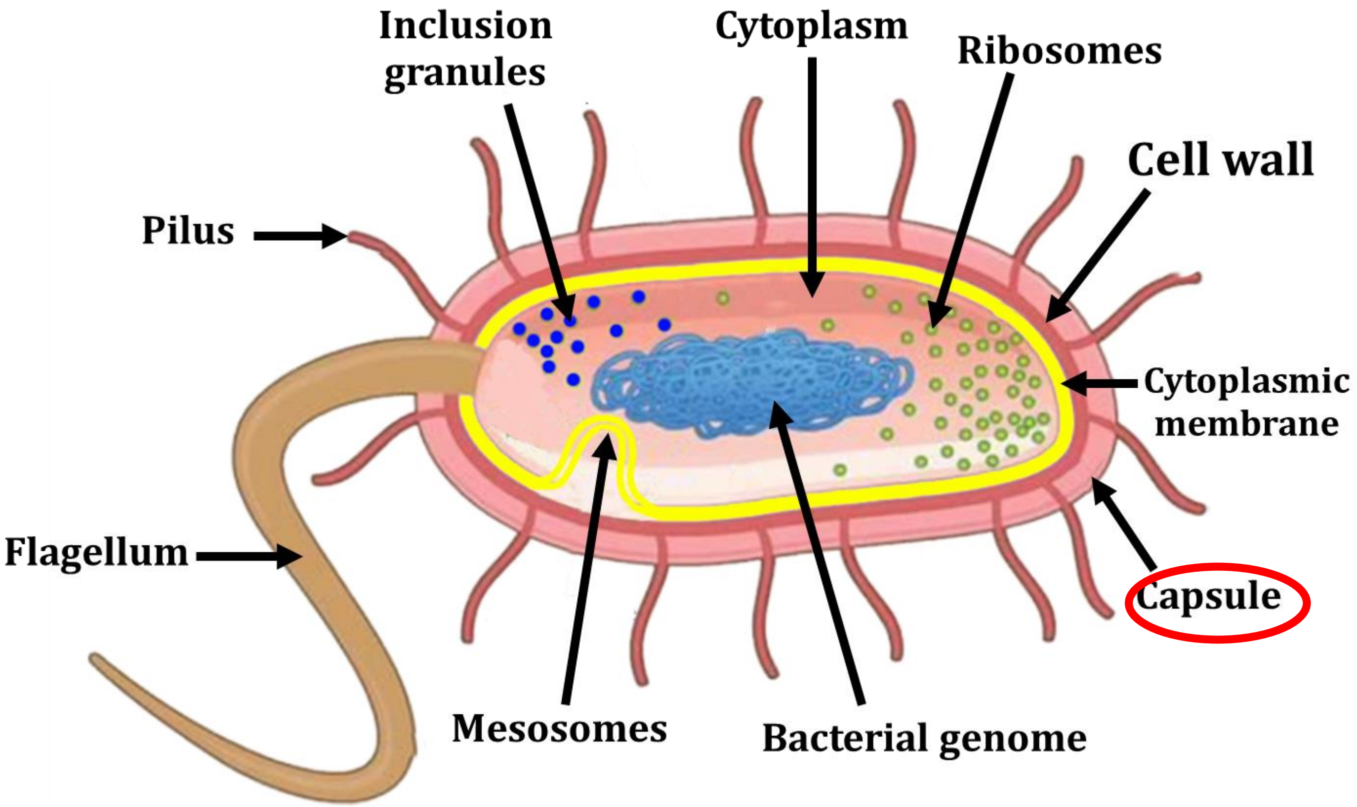
Activate B cells directly → No need for Th

Structure & Examples

Formed of **repeating multiple epitopes**

e.g **Bacterial polysaccharides** : capsule





II) Polysaccharide Ags: T (Thymus) independent Ags

Activate B cells directly → No need for Th

Characters of IR

1) **Activate B cells directly** by **cross linking** multiple BCRs

(No need for Th)

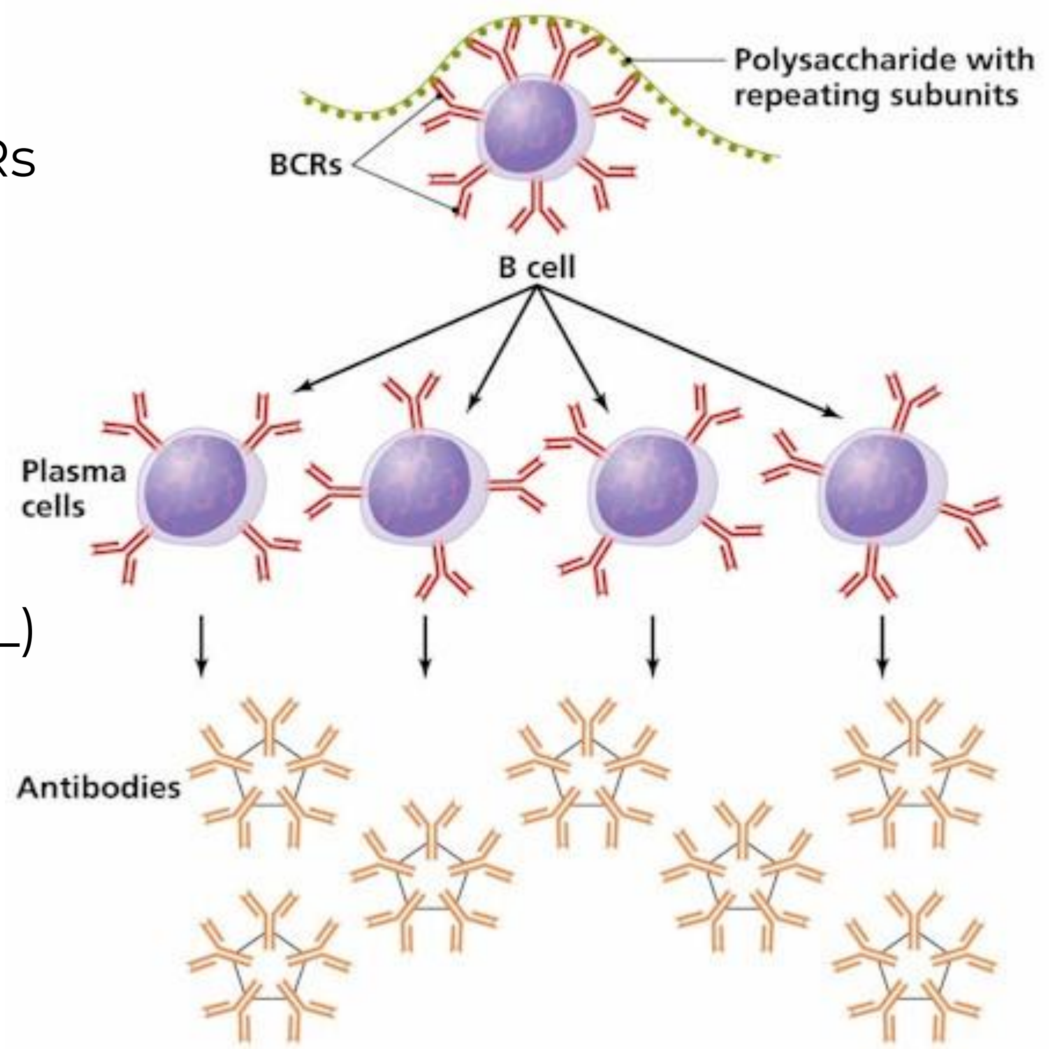
↓

Faster stimulation

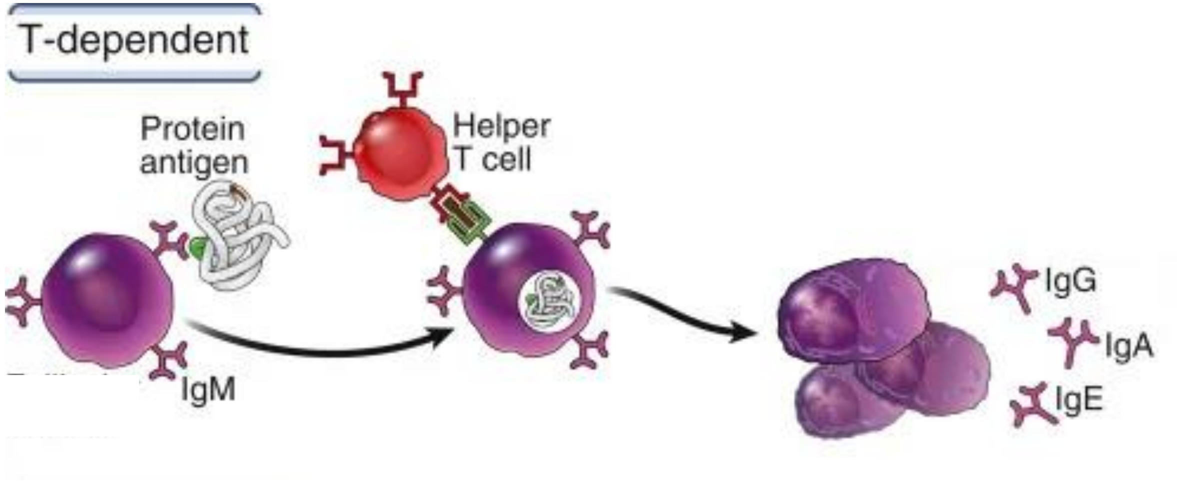
2) Ab classes : **IgM** only

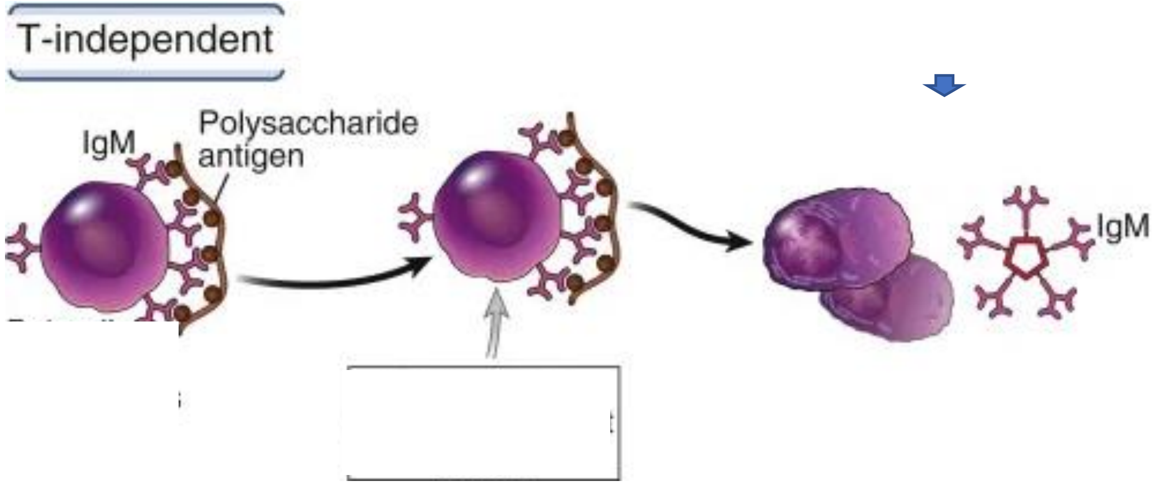
(No class switch due to absence of cytokines & CD40L)

3) No Memory response on 2nd exposure to same Ag



	T cell dependent Ags	T cell independent Ags
Structure & Examples	**Not formed** of repeating epitopes e.g **Proteins**:	Formed of **repeating multiple epitopes** e.g **Bacterial polysaccharides** : capsule
Characters of IR	1) **Need ⊕ of Th cells** (B cell acts as APC)	1)**Activate B cells directly** by **cross linking** multiple BCRs (No need for Th) → **Faster stimulation**
	2) Ab classes	
	IgM & IgG, A , E (class switch)	**IgM** only (No class switch due to absence of cytokines & CD40L)
	3) Memory response on 2nd exposure to same Ag	
	Present	**No**





Quiz 1

Which of the following characterizes bacterial capsules?

A. Induce production of IgG

B. On reexposure to them, the immune response will be faster

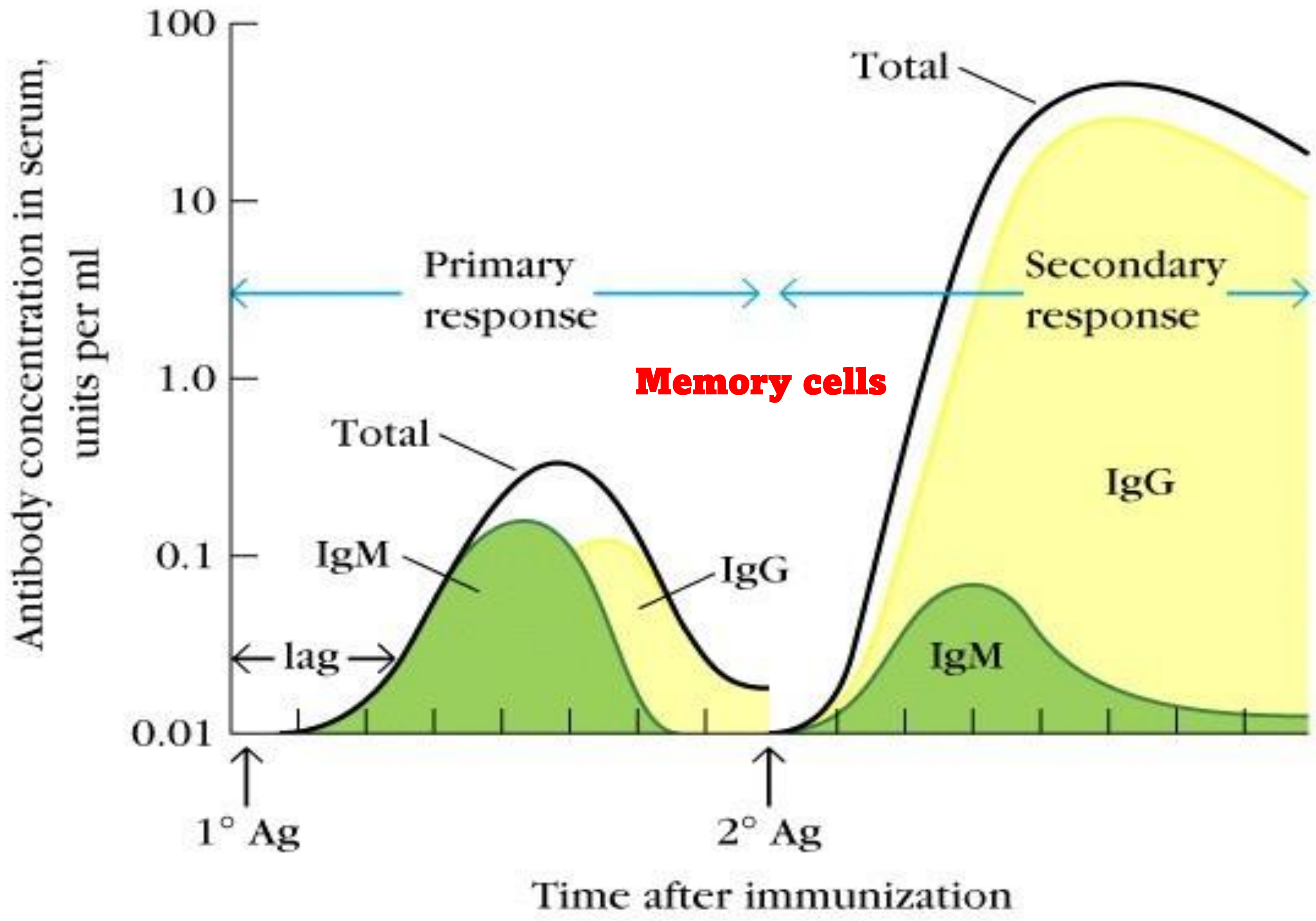
C. On reexposure to them, the immune response will be stronger

D. Are formed of multiple non repeating epitopes

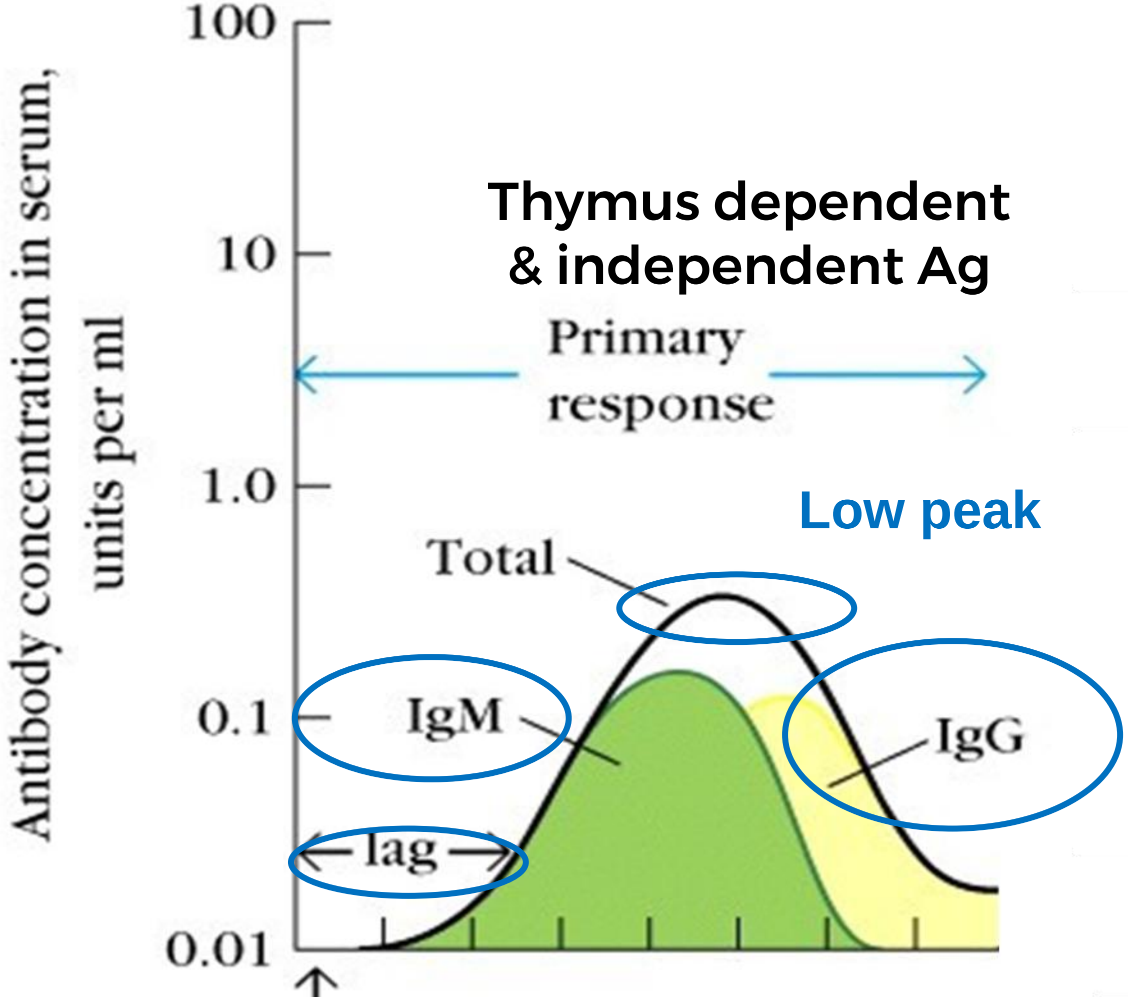
E. Activate B cell directly without T cell help

E

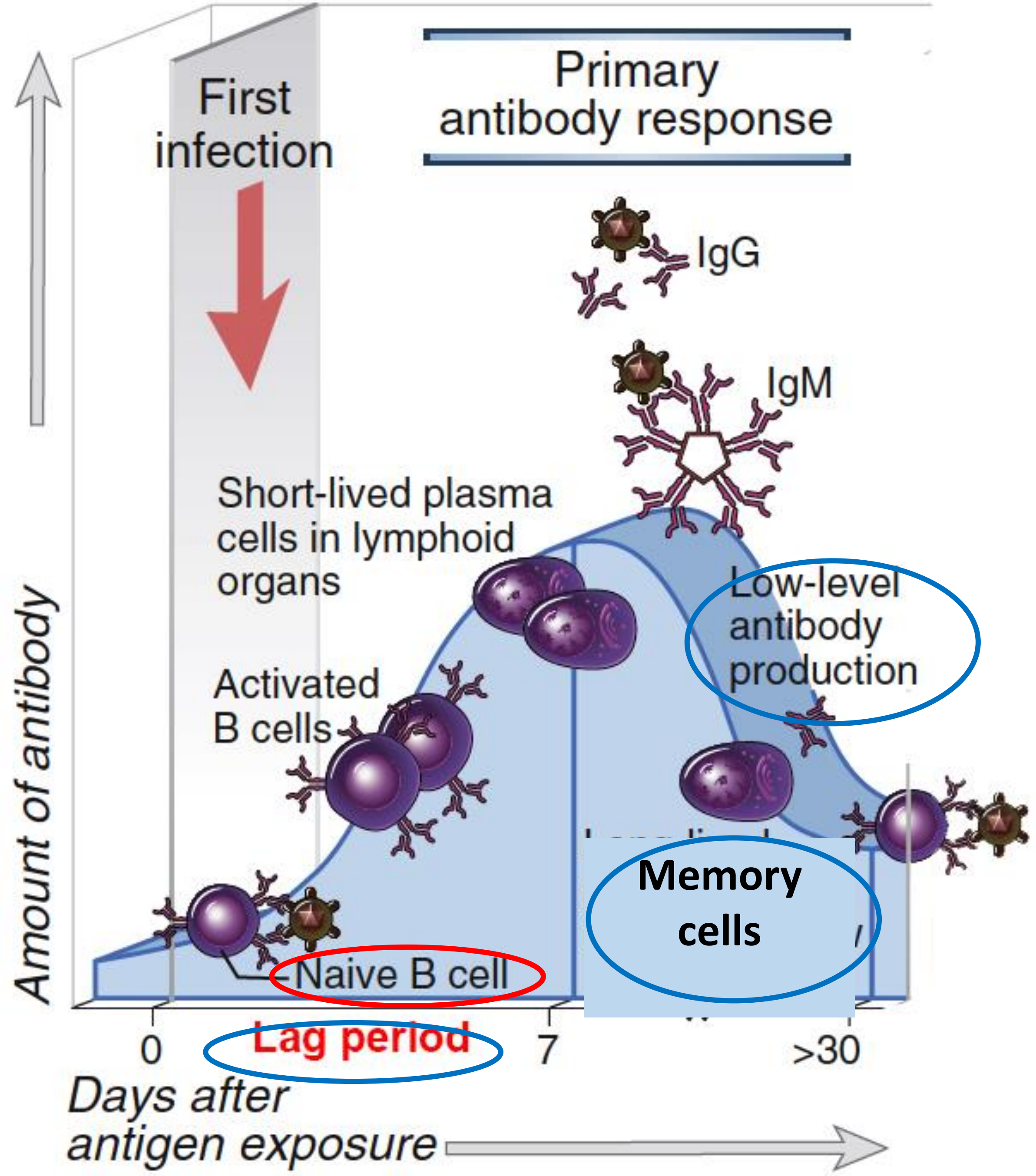
1RY IMMUNE RESPONSE VS 2RY IMMUNE RESPONSE



Thymus dependent & independent Ag



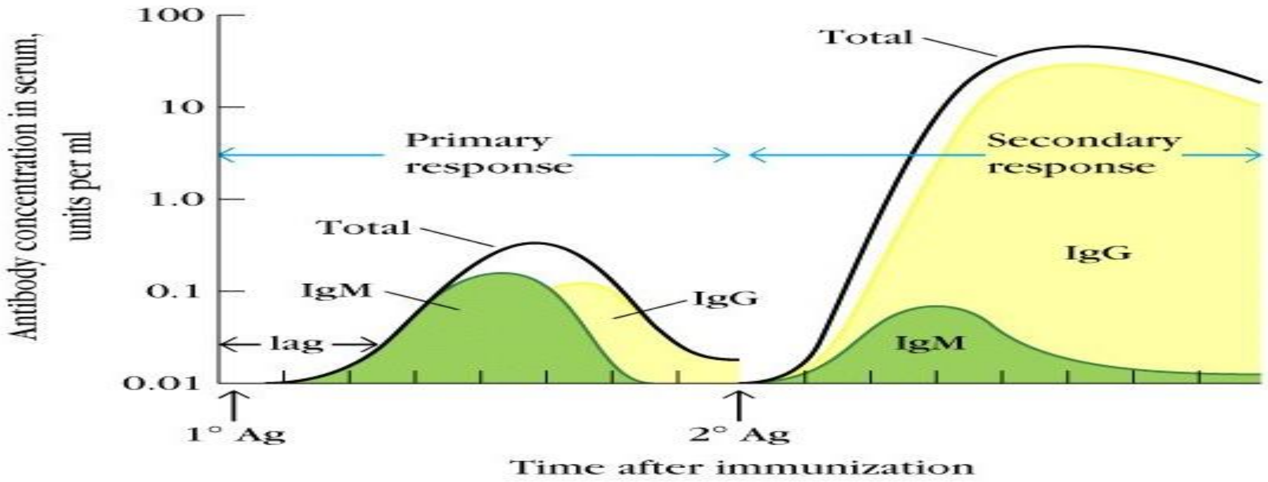
Low peak


First infection
Primary antibody response
IgG
IgM
Short-lived plasma cells in lymphoid organs
Activated B cells
Low-level antibody production
Memory cells
Naive B cell
Amount of antibody
0
Lag period
7
>30
Days after antigen exposure

In thymus independent Ags

- Lag period is shorter
- No memory cells

	1ry Immune response	2ry Immune response
Ag	- **1st exposure** to Ag - T cell **dependent & independent Ags**	- **Reexposure** to the same Ag - T cell **dependent Ags only**
Responding B cell	**Naïve B cells**	**Memory** B cells
Lag period	**7 – 10 days**	**1 – 3 days**
Ab level (peak response)	**Low** concentration continues to ↑ for several weeks ➜ very low levels)	**High** (persists much longer)
Main isotype produced	**IgM** (1st produced , but ↓ earlier than IgG)	**IgG**



Practical applications of 2ry immune response

↓

Induction of memory cell

1- 2nd exposure to same microbe

↓

No disease

2-Vaccine (killed microbe)

↓

Exposure to **microbe (2nd exposure)** will activate **memory cells**

Immunoglobulin isotypes

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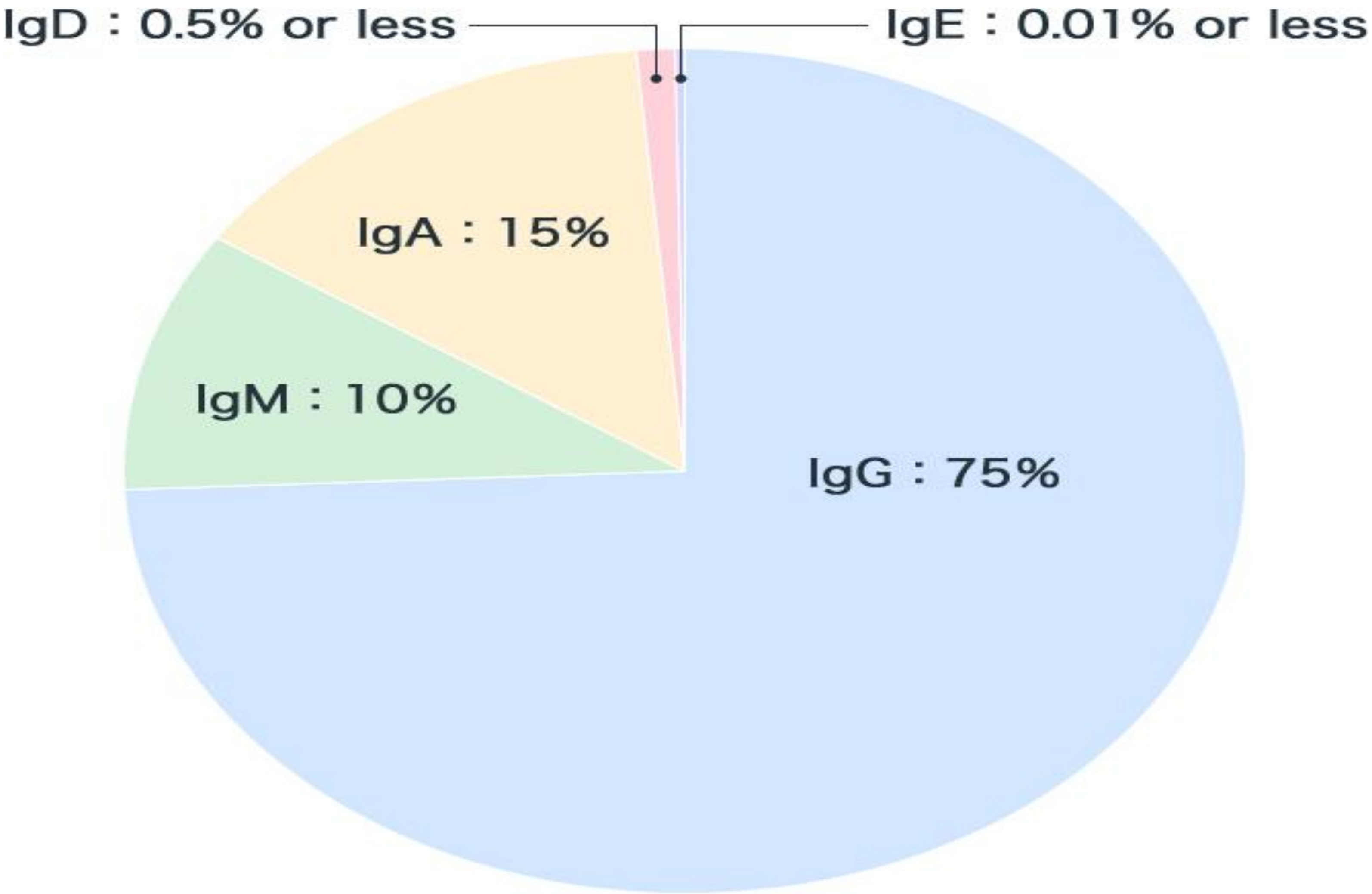
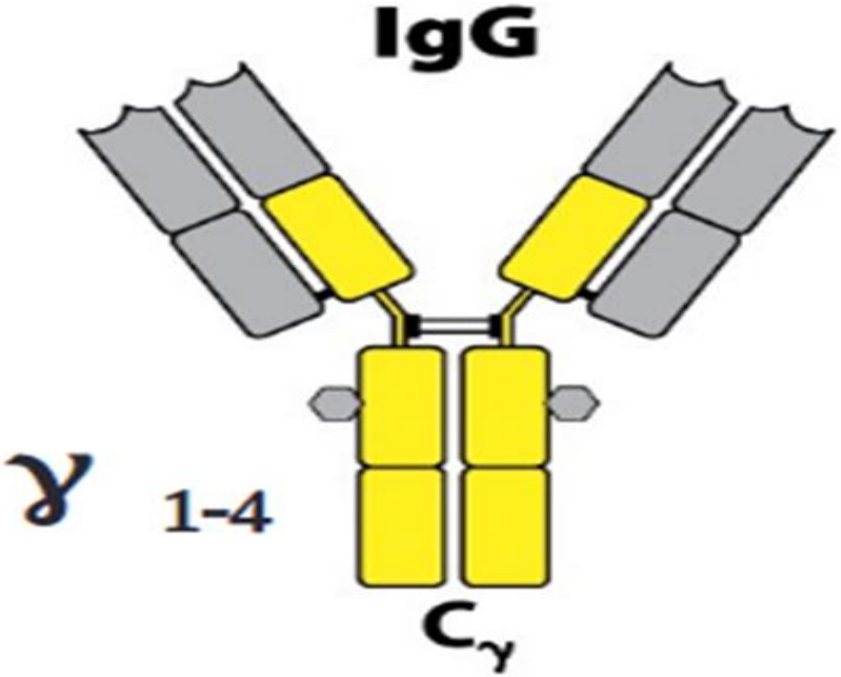
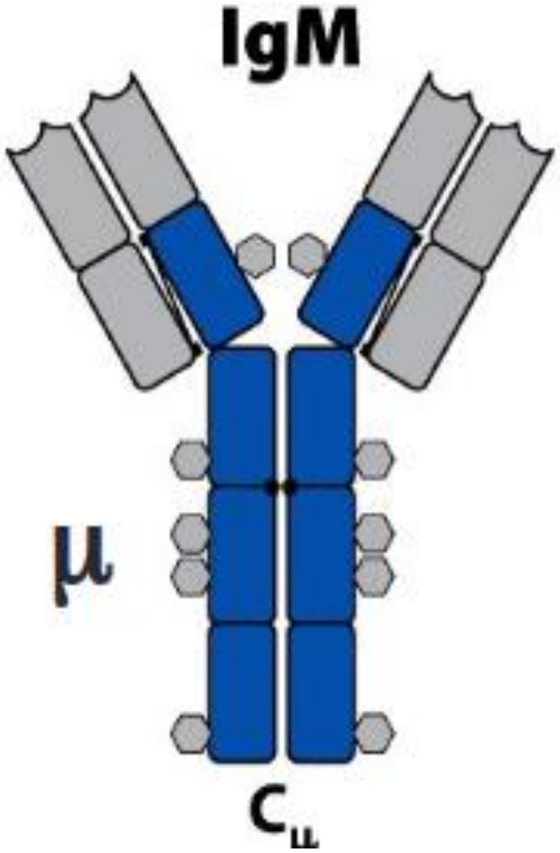
	IgG	IgM
Concentration (of total Ab serum concentration)	75% (most abundant)	10%

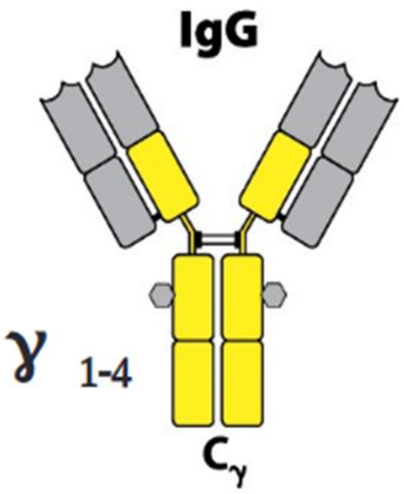


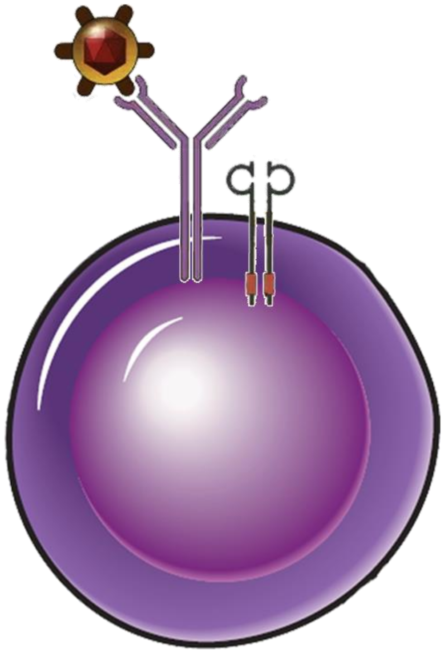
	IgG	IgM
Structure	**Heavy chain**	
	γ chain	μ chain

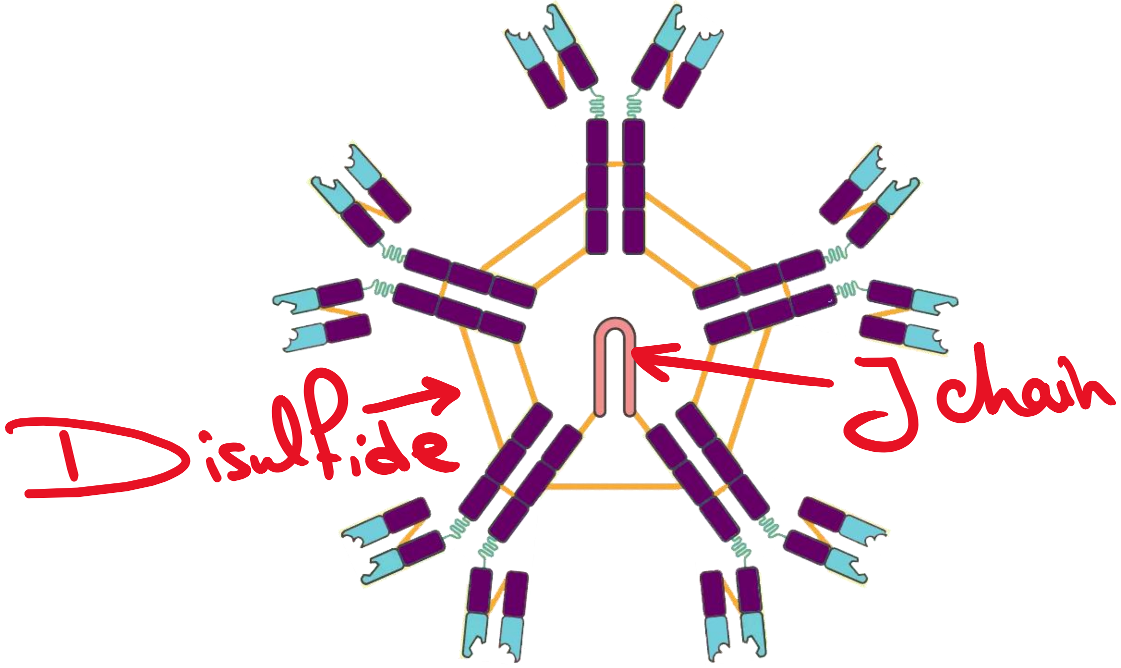




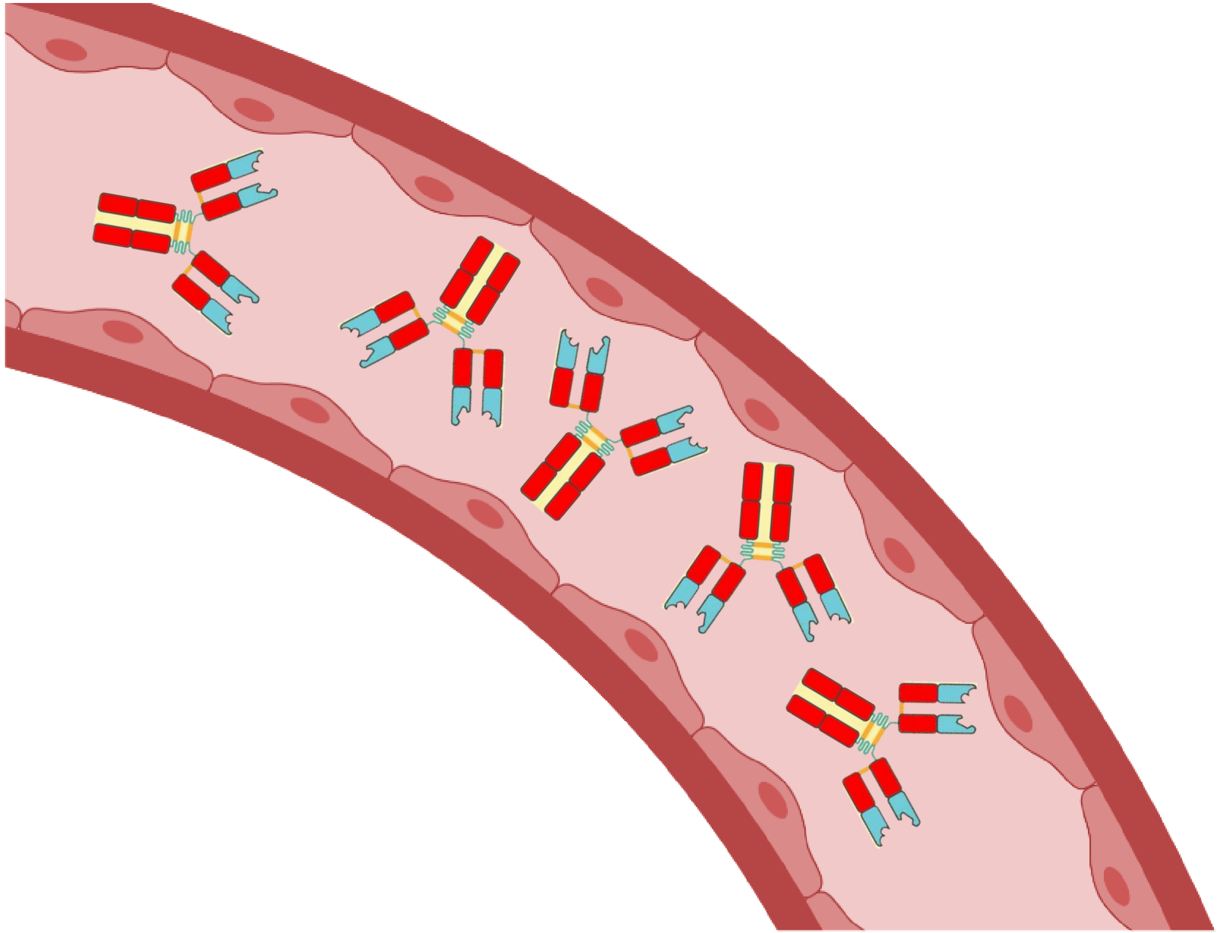
	IgG	IgM
Structure	**Molecular forms & Molecular weight**	
	Monomer → Lowest MW	**1) Monomer (membrane bound) :** BCR **2) Pentamer (serum form):** 5 monomer joined by **a) Disulfide bonds** **b) J chain: Links 2 of the Fc** → **Highest MW** ➥ **Highest valency : 10** Ag binding sites ➥ **Most efficient in complement activation & agglutination**

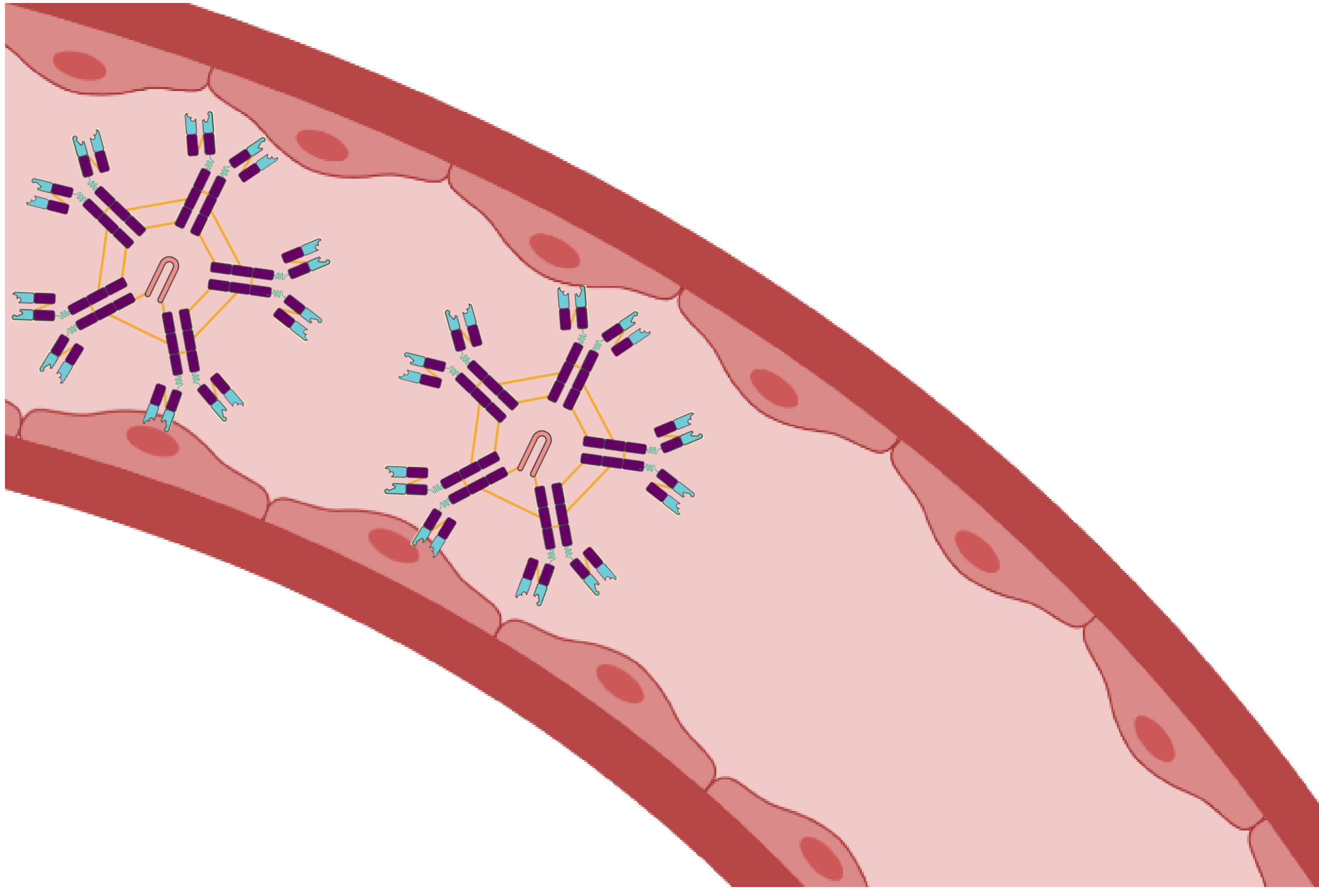




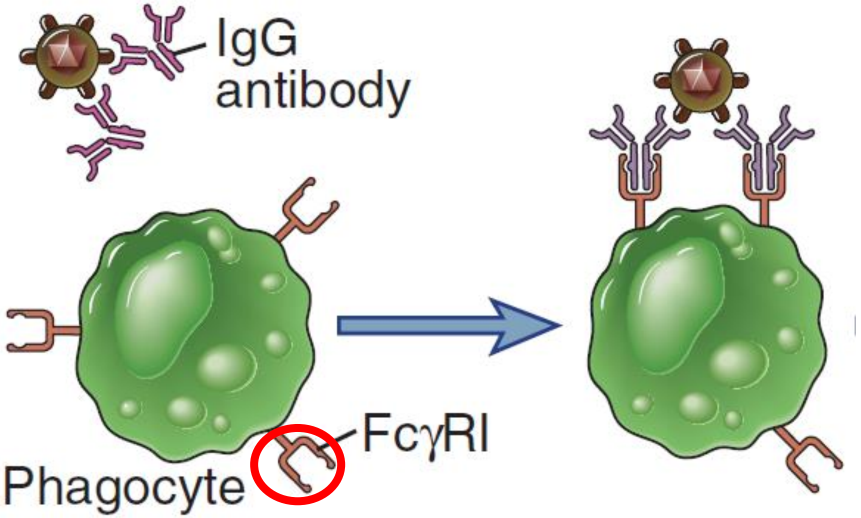


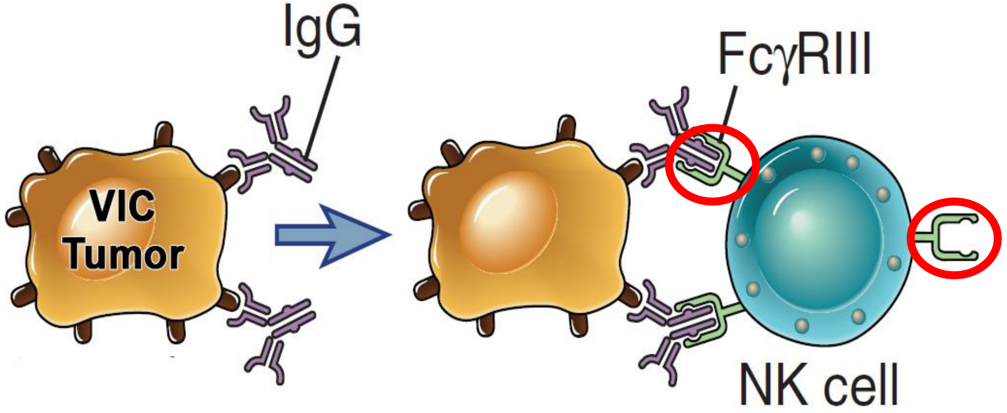
	IgG	IgM
Distribution	Diffuses easily extravascular	Doesn’t diffuse well (due to HMW) → Mostly Intravascular





	IgG	IgM
Binding to immune cells	**Binds to Fc γ R on phagocytes & NK cells**	**No**





Functions of Igs

مرتبطين بخلايا

Only by IgG

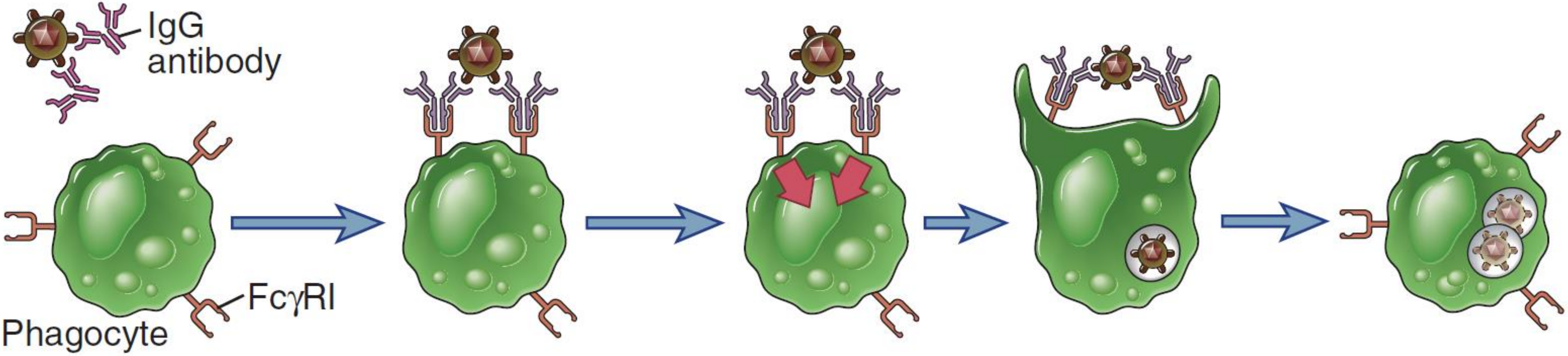
- Opsonization
- ADCC
- Activation of complement
- Neutralization

IgG

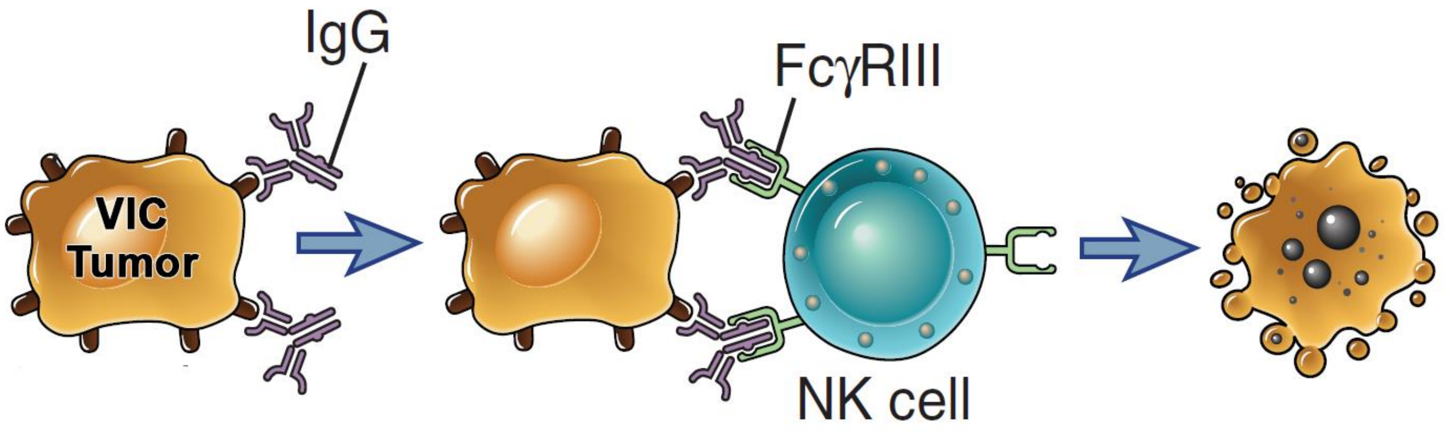
بتاع كله

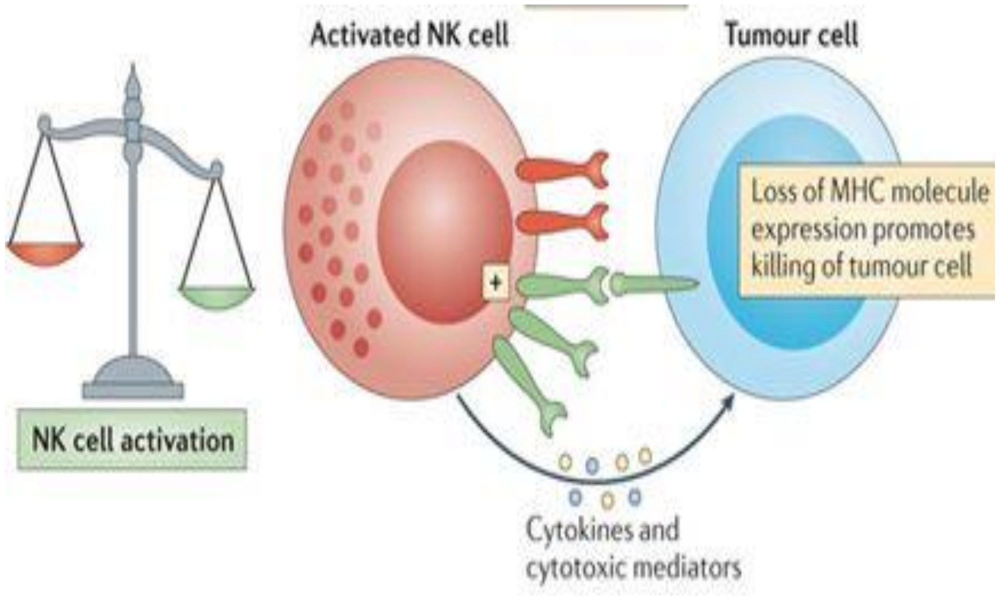
	IgG	**IgM**
Effector mechanisms	**1) Opsonization**	
	IgG (opsonin) coats organism ↓ Binds to **Fcγ R** on phagocytes (MQ & neutrophils) ↓ Facilitates **ingestion & IC killing**	**NO**

opsonin

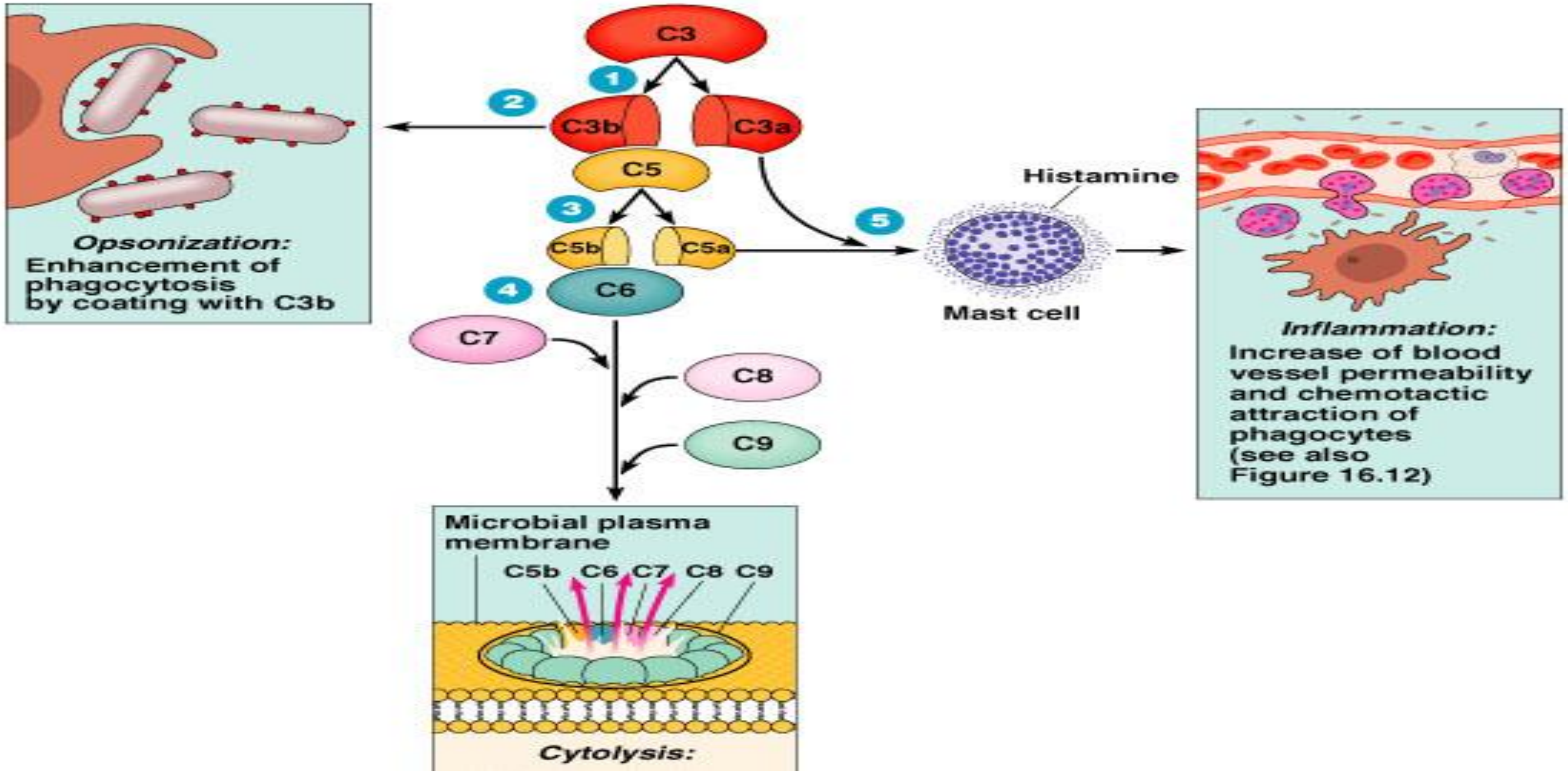


	IgG	IgM
Effector mechanisms	**2) ADCC (Ab dependent cellular cytotoxicity)**	
	IgG coats **target cells** (**virally infected** or **tumor** cell) ↓ **Binds to Fcγ R** on **NK** or **phagocytes** ↓ Release of granular toxic mediators (**EC killing**)	**NO**



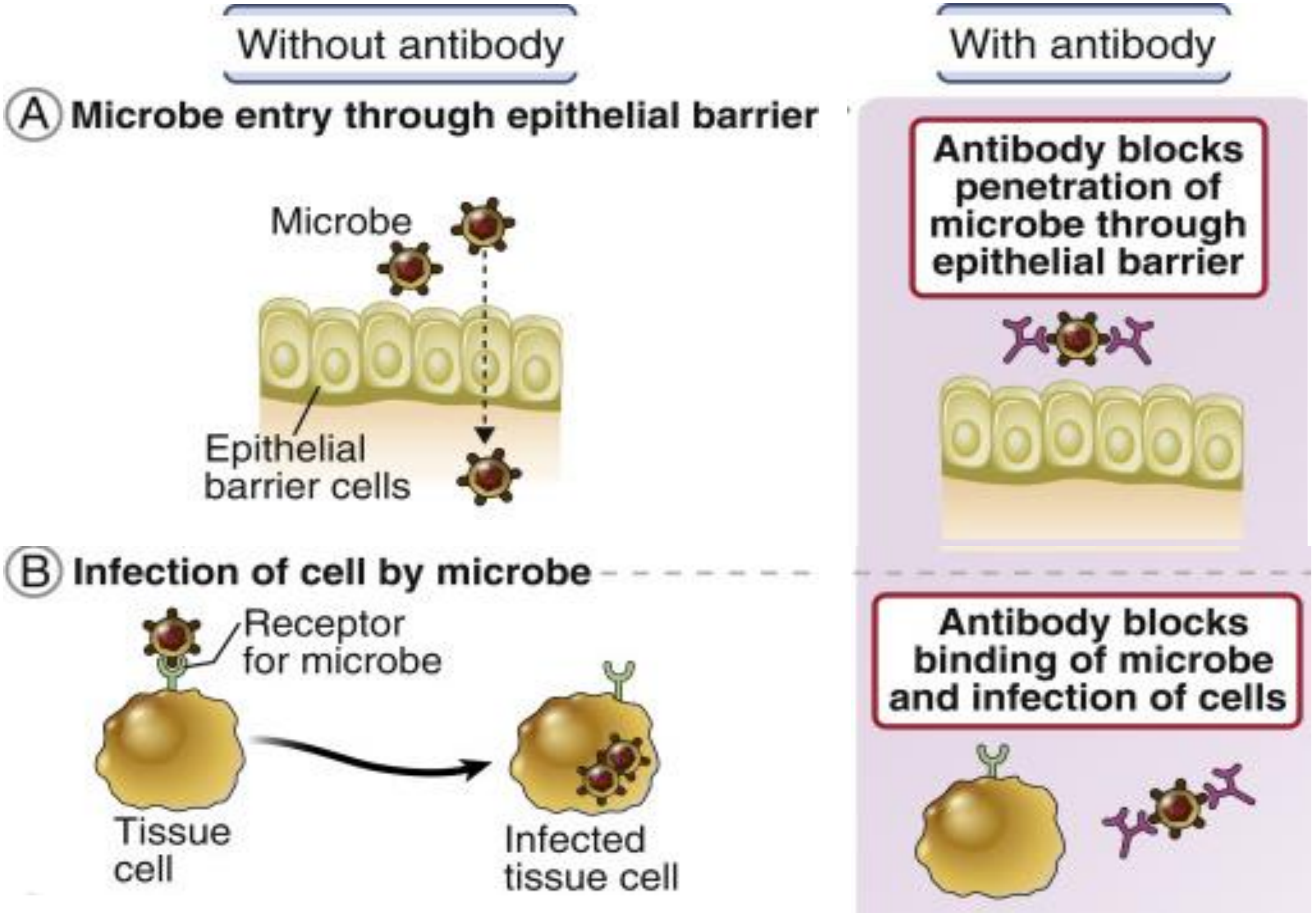

Activated NK cell
Tumour cell
Loss of MHC molecule expression promotes killing of tumour cell
+
NK cell activation
Cytokines and cytotoxic mediators

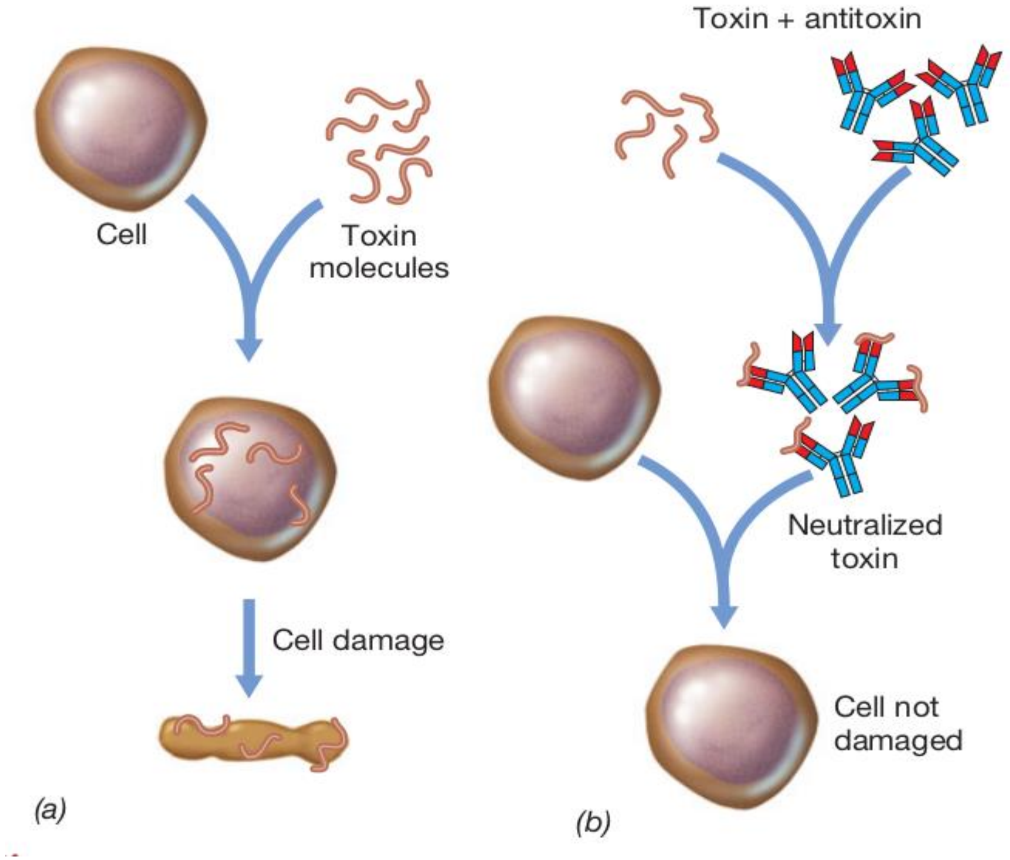
	IgG	IgM
Effector mechanisms	**3) Complement activation : by classical pathway** → **Opsonization & Lysis of organism**	
	Yes	Most efficient



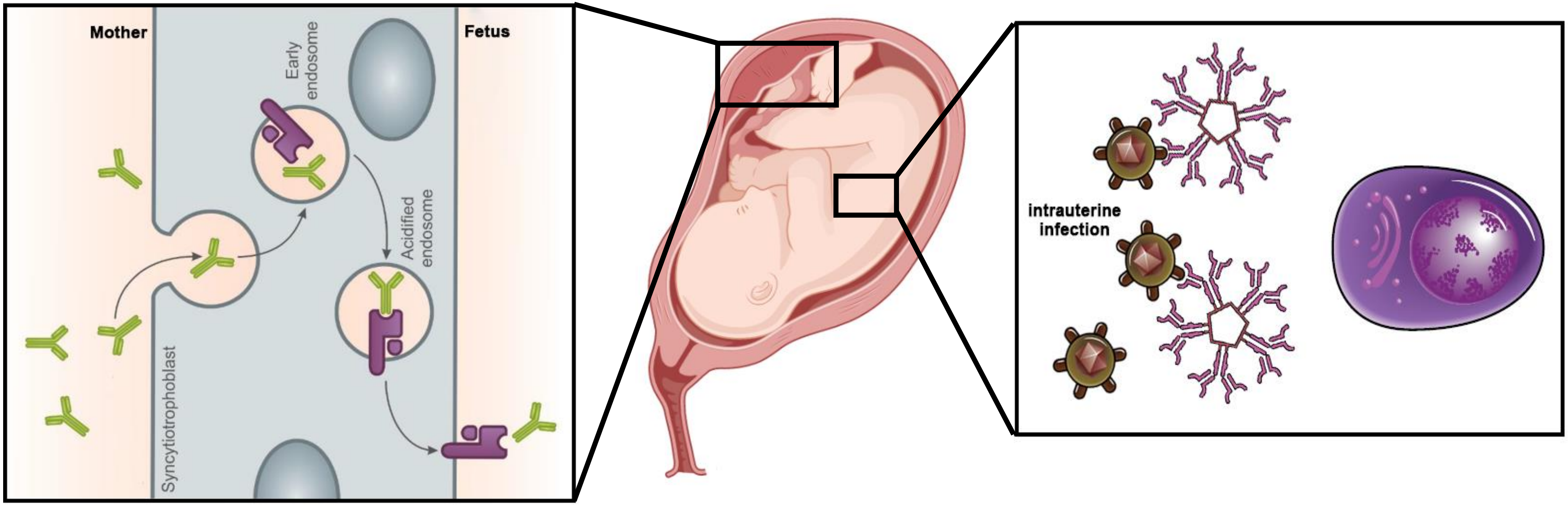
C3
1
2
C3b
C3a
C5
3
C5b
C5a
4
C6
5
C7
C8
C9
Histamine
Mast cell
Opsonization:
Enhancement of phagocytosis by coating with C3b
Inflammation:
Increase of blood vessel permeability and chemotactic attraction of phagocytes (see also Figure 16.12)
Microbial plasma membrane
C5b C6 C7 C8 C9
Cytolysis:

	IgG	IgM
Effector mechanisms	**4) Neutralization**	
	IgG (most efficient) **binds to viruses, EC bacteria & toxins** ➥ **Prevents their binding to target cell**	**Yes**


Without antibody
With antibody
A Microbe entry through epithelial barrier
Microbe
Epithelial barrier cells
Antibody blocks penetration of microbe through epithelial barrier
B Infection of cell by microbe
Receptor for microbe
Tissue cell
Infected tissue cell
Antibody blocks binding of microbe and infection of cells



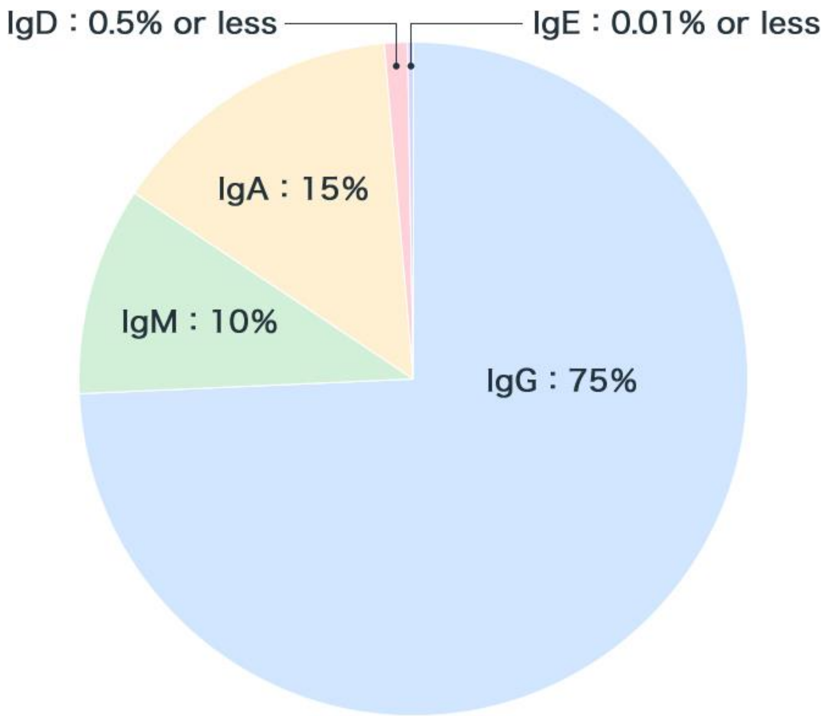
	IgG	**IgM**
Other properties	**Placental passage**	
	Only Ig that crosses the placenta ↓ **Immunity to fetus & neonate**	No, but is the **1^{st} Ig synthesized by fetus** ↓ Indicates **intrauterine infection** if ↑ in neonates



Ig A

Concentration

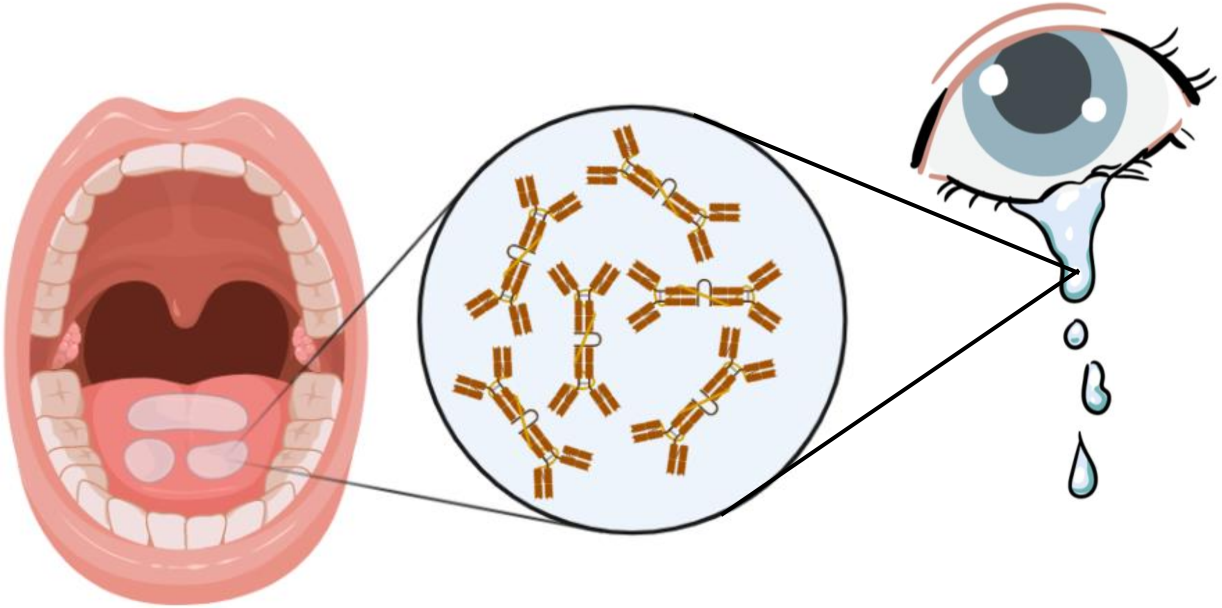
15% of total serum Igs

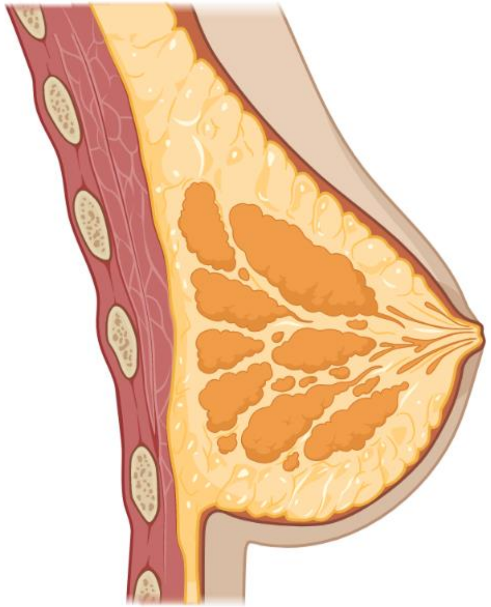


Site & Characters

Secretory IgA : Main Ab in secretions

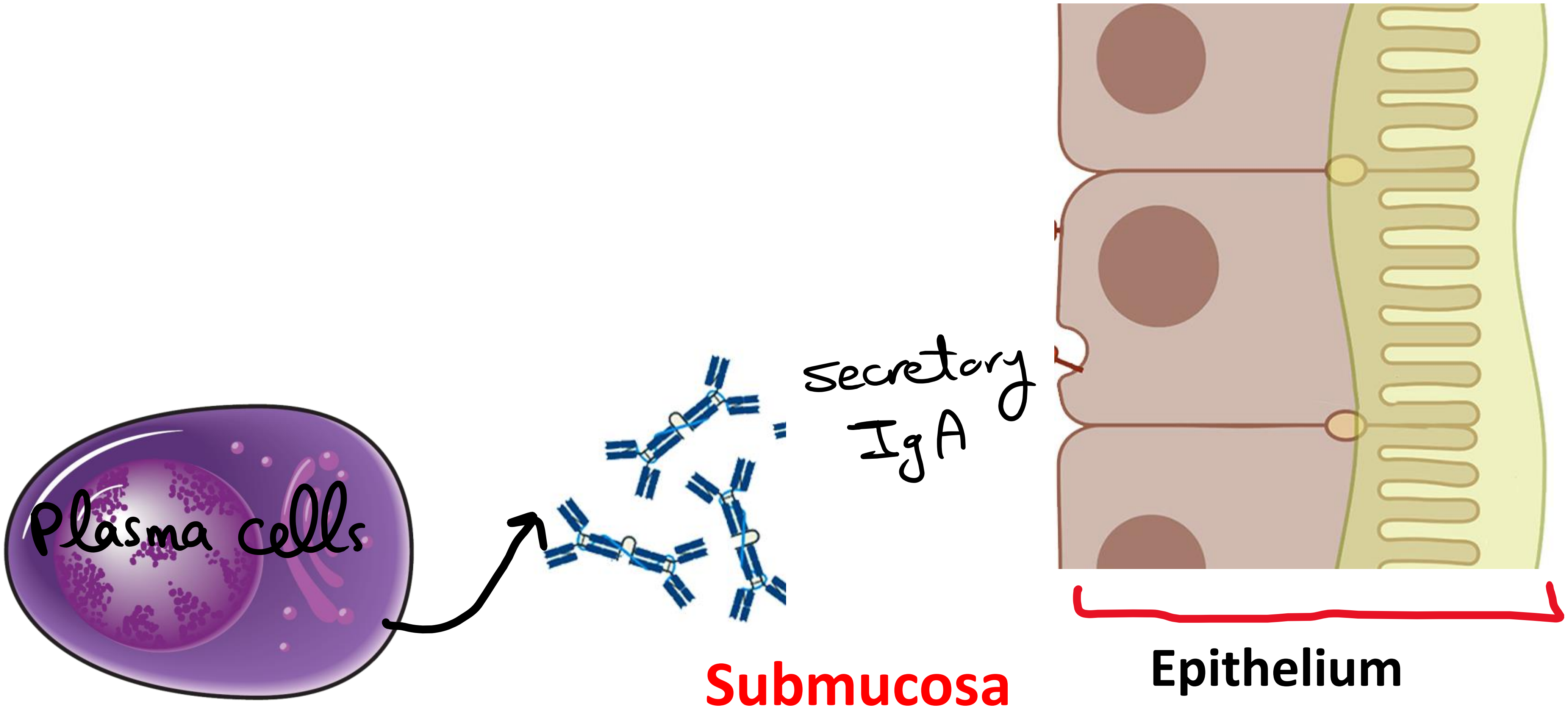
- Saliva & tears
- Mucus of RT & GIT
- Breast milk





Ig A

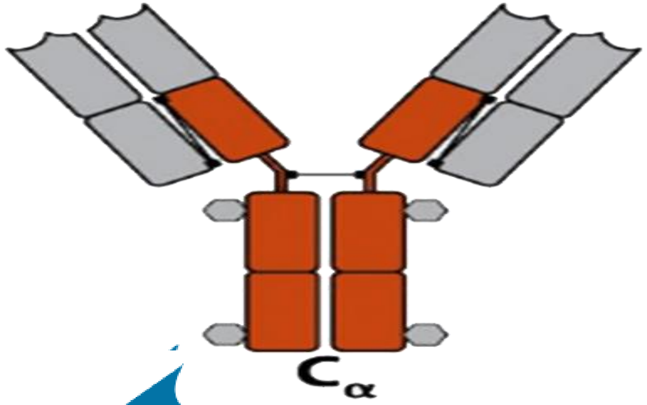
Synthesized by **submucosal plasma cells**



Structure

- **Molecular forms:** الأشكال الجزيئية

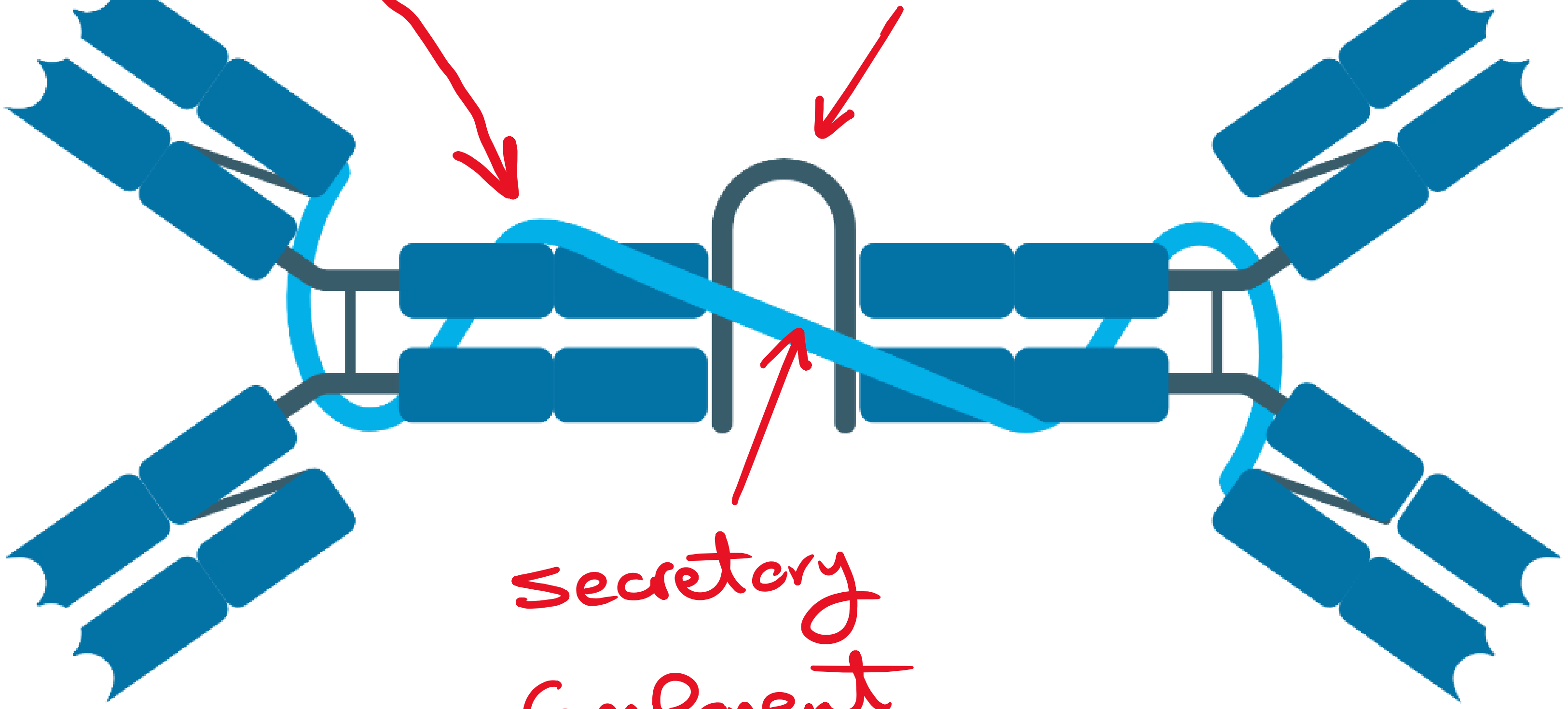
- **Heavy chain: α chain**



Secretory IgA is a dimer:

2 monomers joined by **J chain**

- **Secretory (S) component**



Remember serum IgM

5

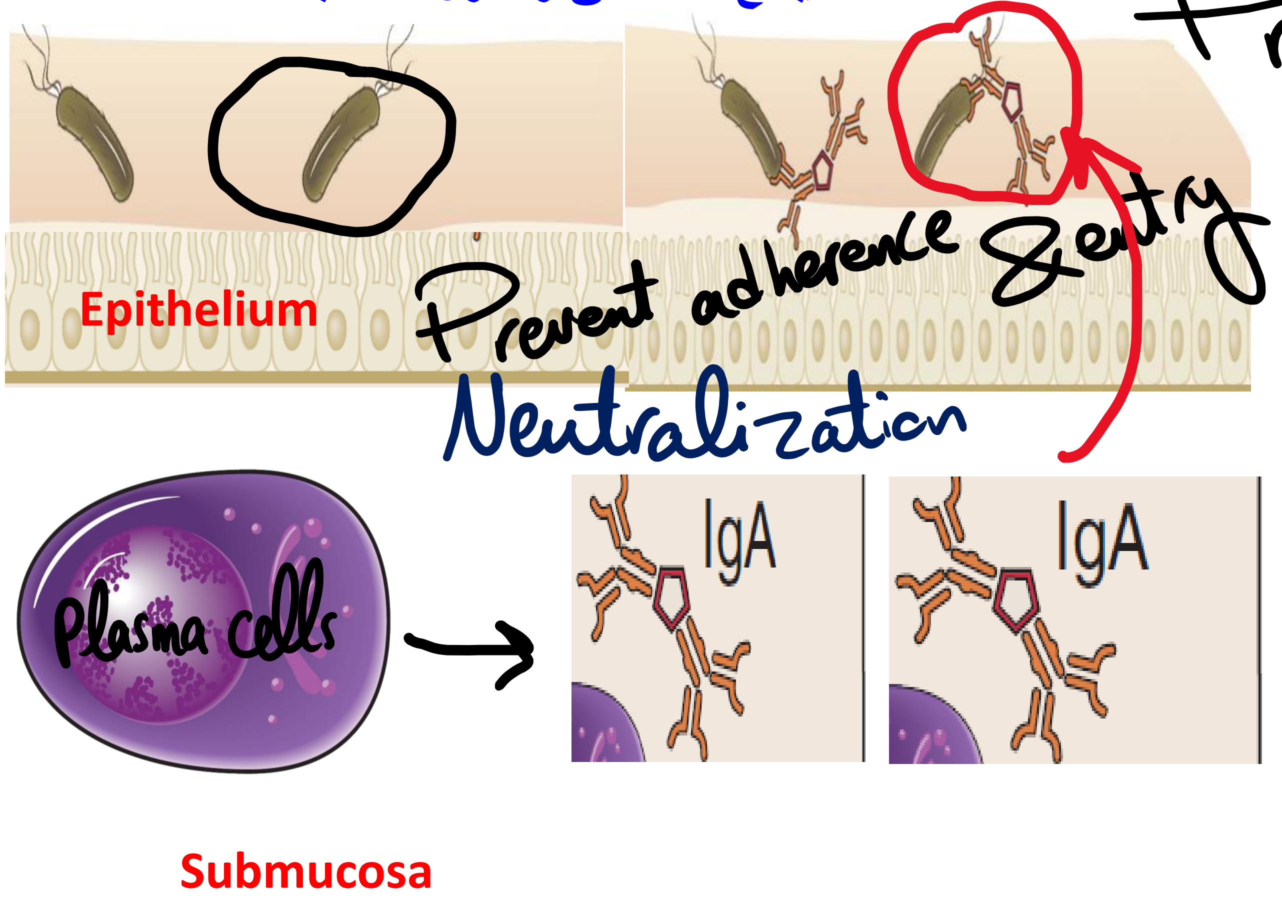
Functions

Local mucosal immunity المناعة المخاطية الموضعية حارس بوابة الجسم

Neutralizes bacteria & viruses in mucosa
↓
Prevent their adherence & entry in tissues

يمنع الالتصاق ودخول الانسجة

Present in milk المولود حديثا
↓
Protects newborn from infection

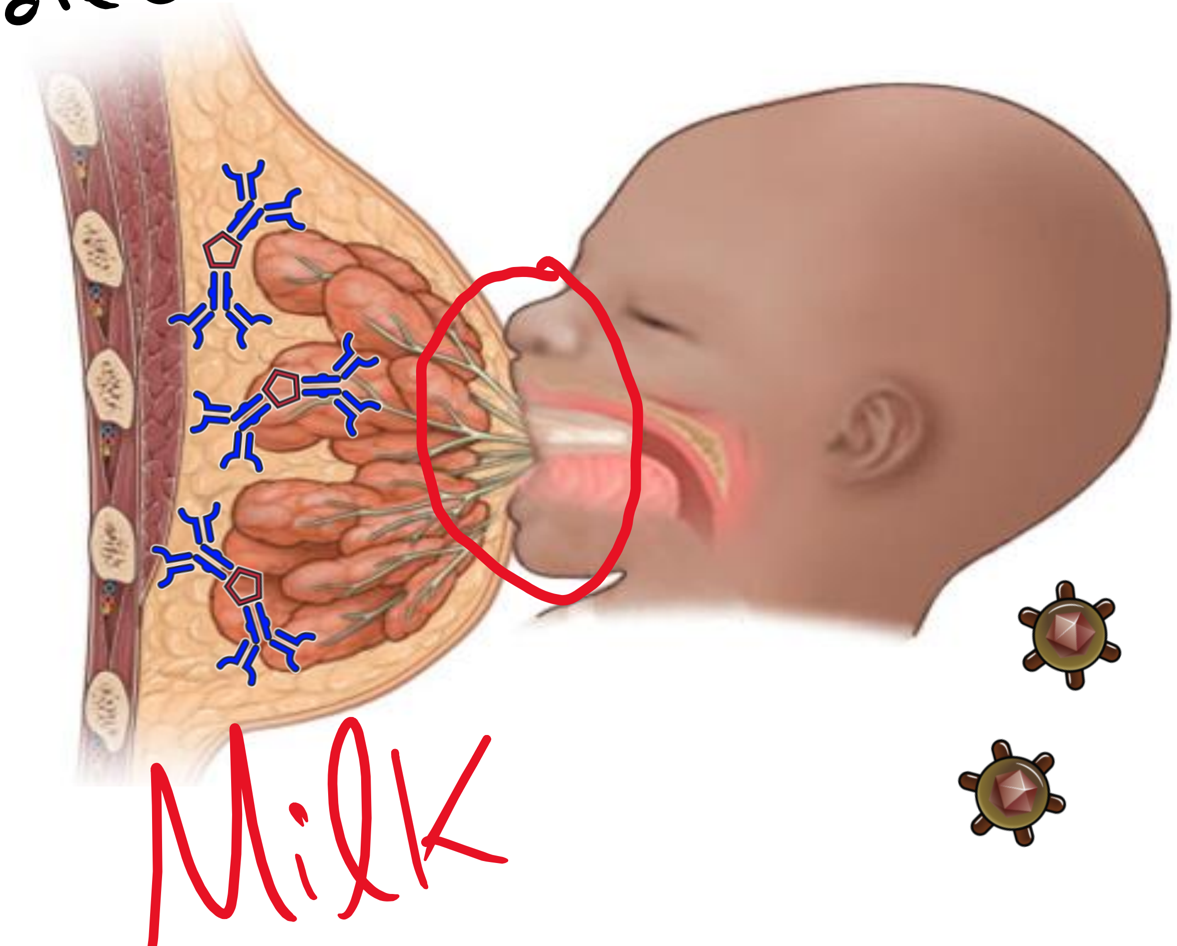


Prevent adherence & entry

Neutralization

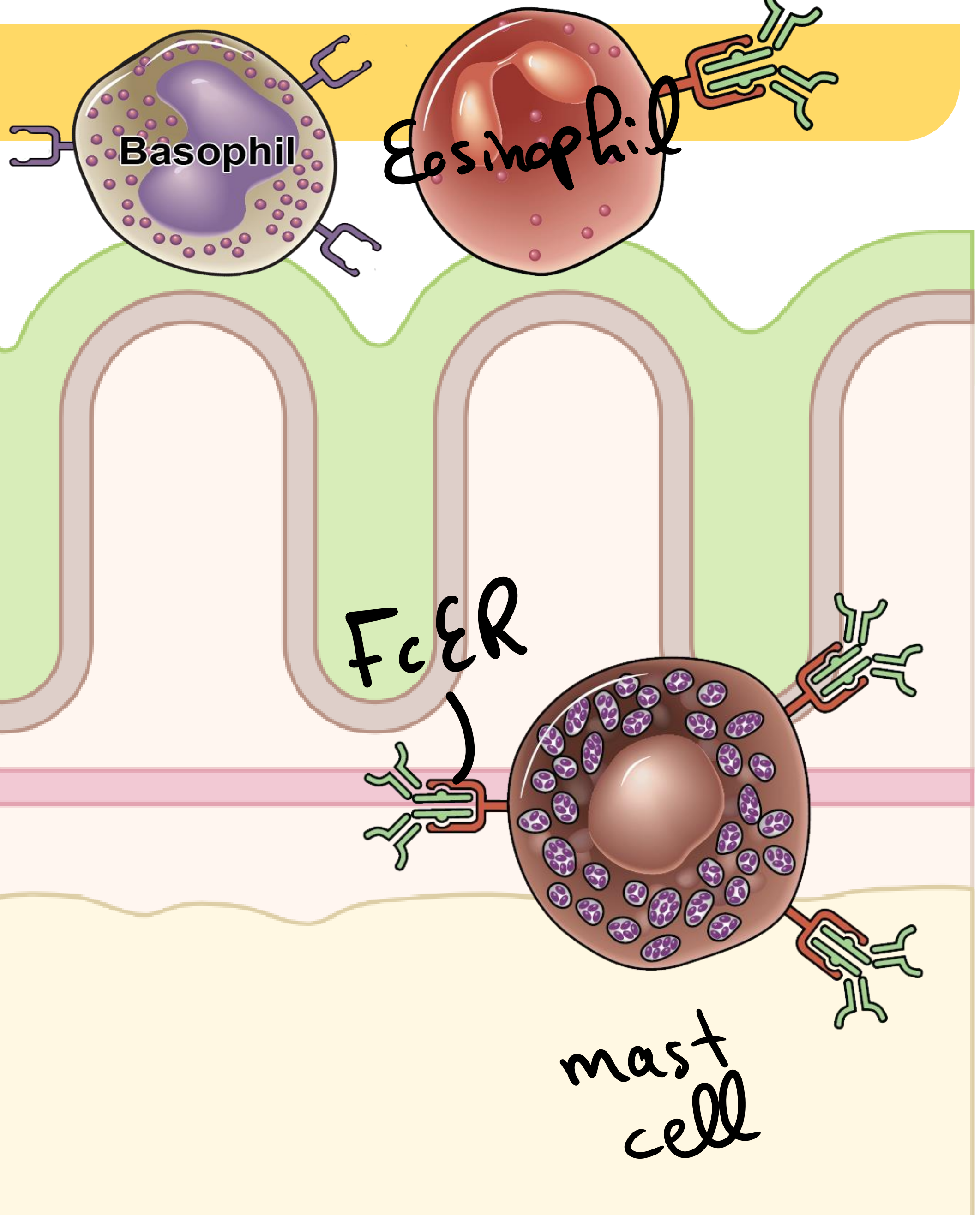
Plasma cells

Protect newborn from infection



Milk

Ig E



Concentration

very low

Site & Characters

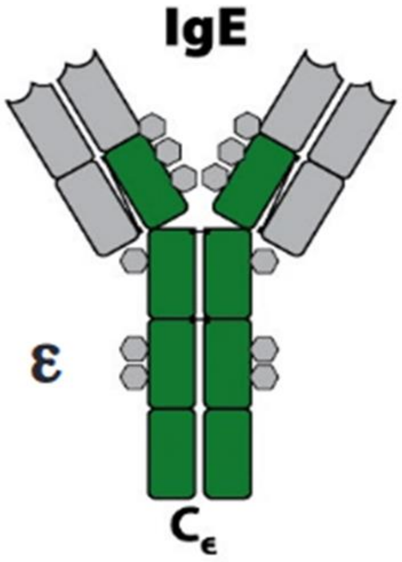
◉ **Mucosa**

◉ Bind to **FcεR** on
- **mast cells**
- **basophils**
- **eosinophil**

Inflammatory cells

involved in allergy

Structure



- **Heavy chain:** ε chain

Ig E

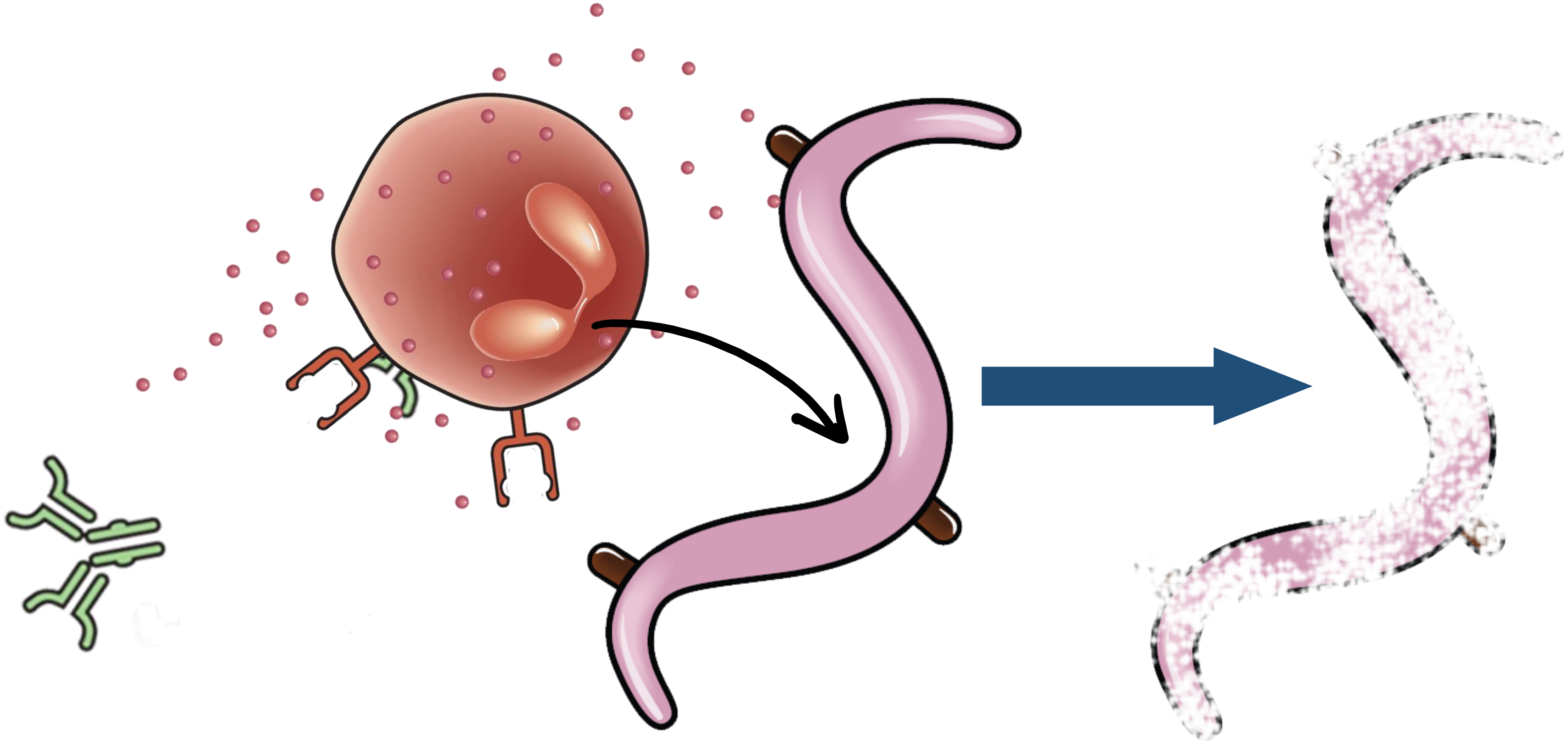
Functions

Remember Th2

1) ADCC (Ab dependent cellular cytotoxicity)

IgE coats **helminths** → Binds to **FcεR** on **eosinophils**

→ releases **toxic protein** → Kill parasite (helminths)



IgE is the main host defense against parasites

Functions

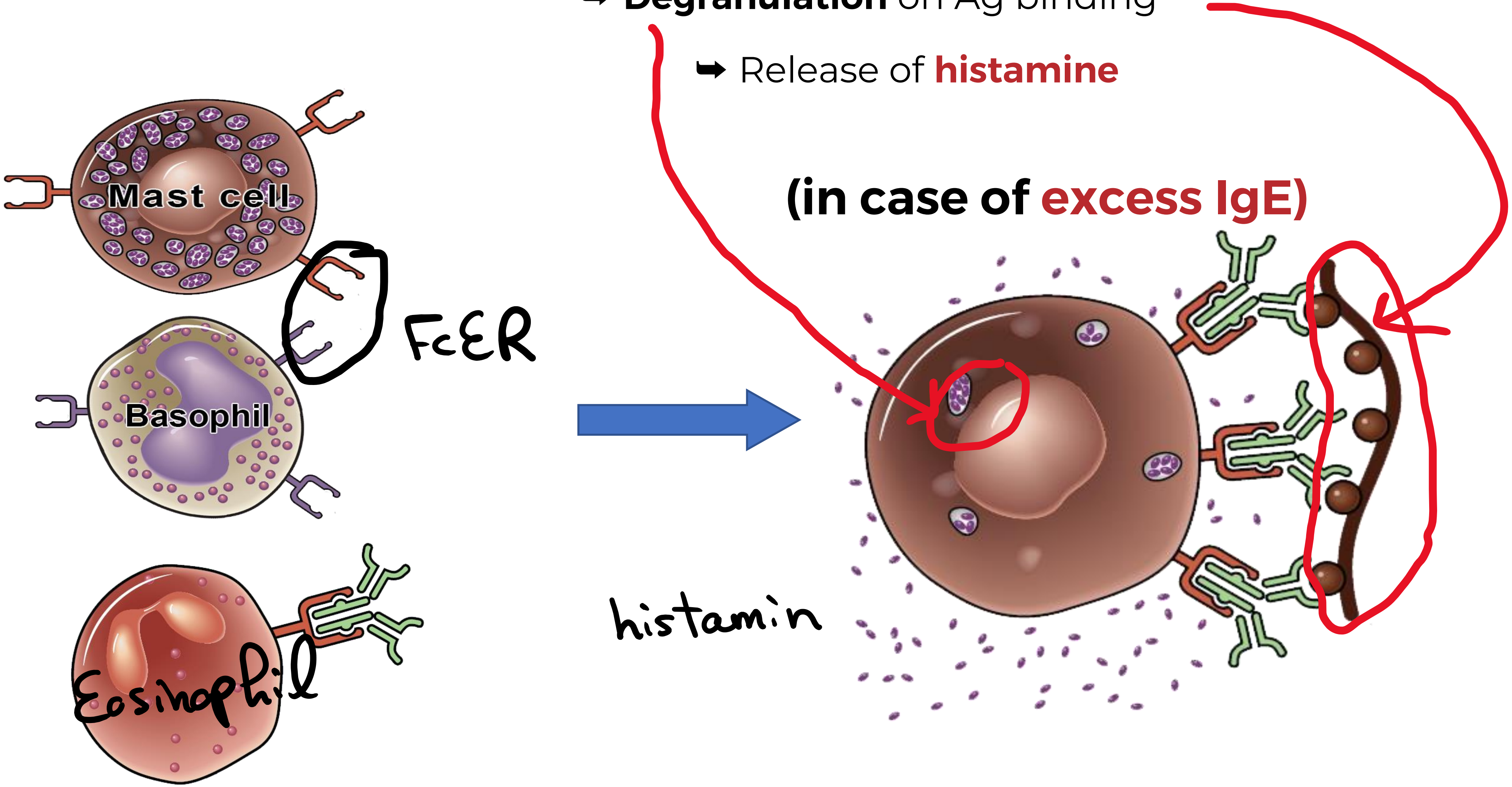
2) Allergic manifestations

IgE binds to **FcεR on mast cells , basophils & eosinophils**

➥ **Degranulation** on Ag binding

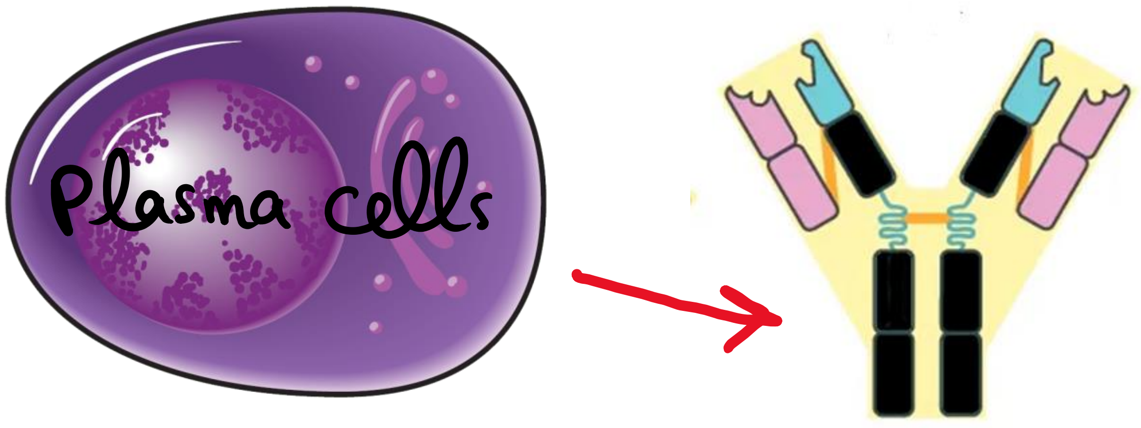
➥ Release of **histamine**

(in case of excess IgE)



Ig D

Concentration **0.2 %** of total serum Igs



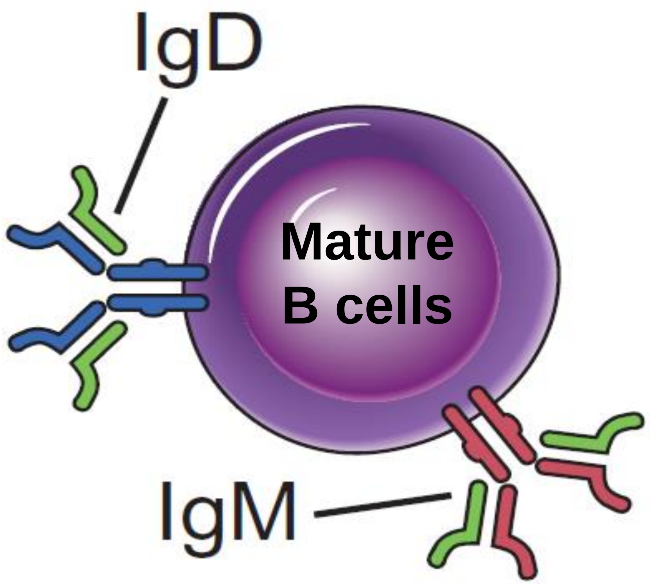
Secreted IgD

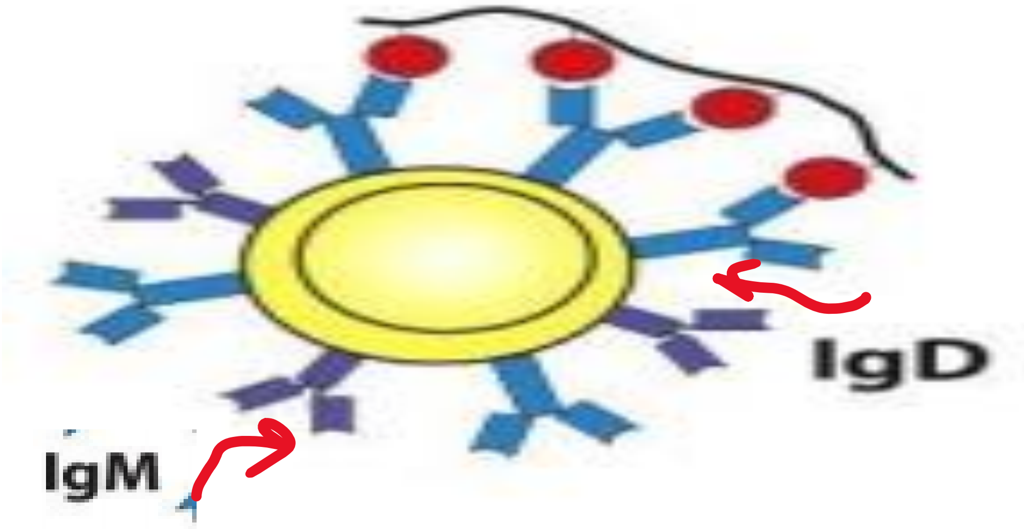
بلا وظيفة

Function

Ag receptor (BCR):

Main membrane bound Ig on mature B cell





Monoclonal Abs(Mc Abs)

Definition

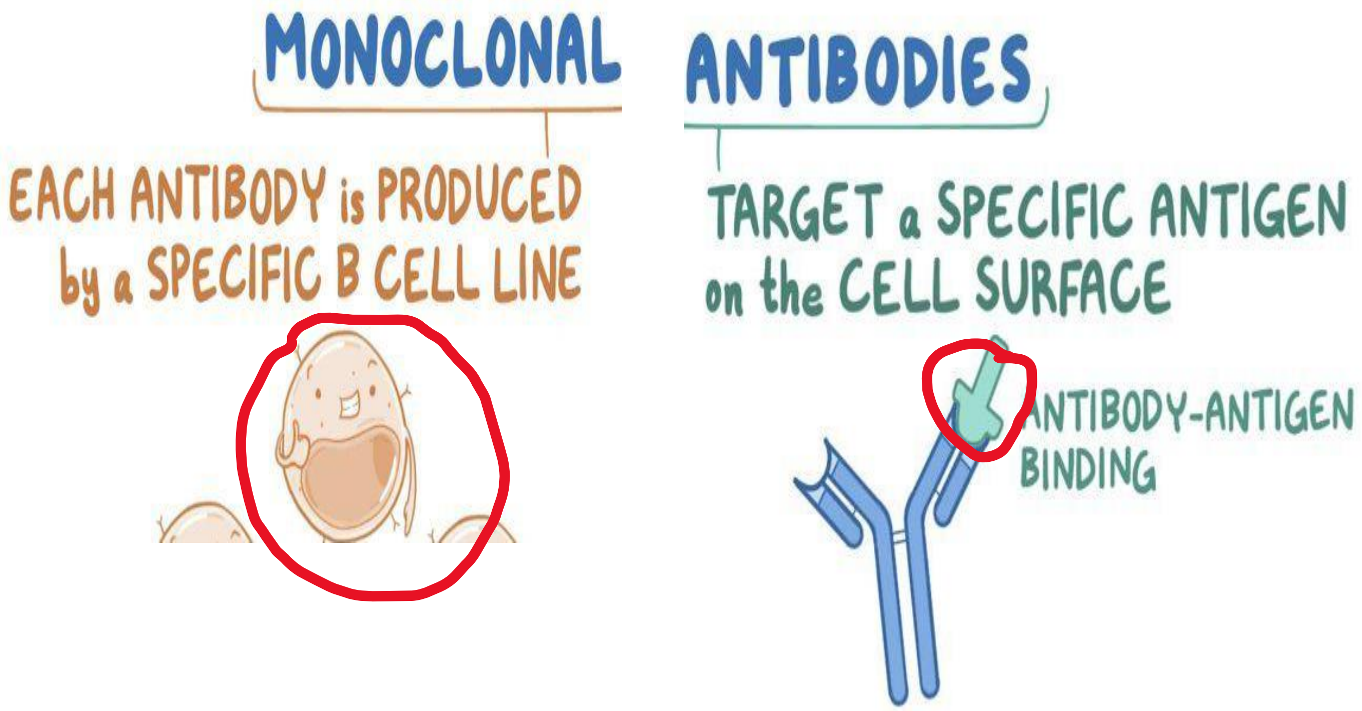
خارج الجسم صناعيا

Ab produced **artificially (in vitro)**

by a **single clone of B cell**

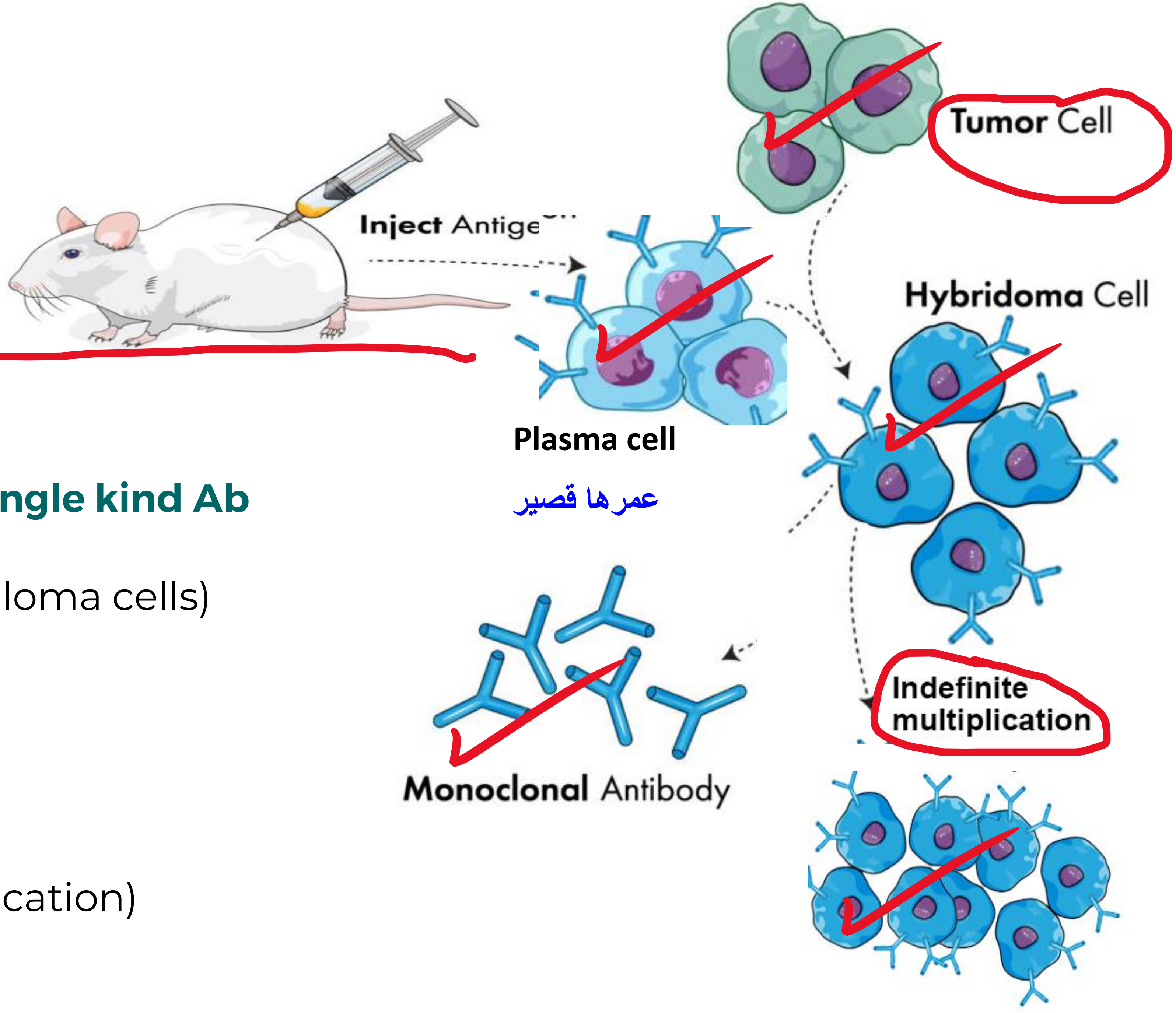
↓

Specific for a **single epitope**


MONOCLONAL
ANTIBODIES
EACH ANTIBODY is PRODUCED by a SPECIFIC B CELL LINE
TARGET a SPECIFIC ANTIGEN on the CELL SURFACE
ANTIBODY-ANTIGEN BINDING

Monoclonal Abs

Method of production



B cells producing the **desired single kind Ab**

are fused with **tumor cells** (myeloma cells)

↓

Production of **hybridoma cells**

↓

1) Secrete the **desired Mc Ab**

2) **Long lived** (indefinite multiplication)